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CROHN'S DISEASE

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IN many of the recent series of Crohn's disease (e.g., van Patter, Bargen, Dockerty, Feldman, Mayo, and Waugh, 1954; Cooke, 1955) a recurrence rate after operation of over 50 per cent has been reported. In the present study a group of 34 patients reported by Armitage and Wilson from Leeds in 1950 has been re-examined and the series extended by the addition of all further cases of Crohn's disease admitted to the Leeds General Infirmary from 1950 to 1956. In all, 108 patients have been included in the present series, of whom half have been followed over five years (*Table I*).

Table I.—108 PATIENTS WITH CROHN'S DISEASE

	TOTAL	DIED POST-OPERATIVELY	DIED LATER OTHER CAUSES	LOST	FOLLOWED LESS THAN 5 YEARS	FOLLOWED MORE THAN 5 YEARS
History less than 1 month (Acute Crohn's)	37	1	1	7	11	17
History 1 month to 2 years (Subacute Crohn's)	39	4	2	5	10	18
History more than 2 years (Chronic Crohn's)	30	3	1	—	9	17
History unknown duration	2	1	—	—	1	—
Total	108	9	4	12	31	52

Nomenclature.—The name Crohn's disease (Crohn, Ginzburg, and Oppenheimer, 1932) is used in this report as it is felt that even the least specific of the non-eponymous names ('regional enteritis', the name used by the Mayo Clinic workers) is too restrictive to describe a disease which sometimes shows itself in a diffuse and not a regional inflammation.

Definition.—In order to unify this series as much as possible I have excluded cases not conforming to a provisional definition of Crohn's disease as a chronic inflammatory disease of the gastro-intestinal tract of unknown aetiology, usually manifesting itself in the form of localized thickening of bowel wall, with a strong tendency to recurrence which may be more diffuse than the original lesion.

This definition excludes cases of solitary ulcers of jejunum or ileum, intestinal tuberculosis, chronic ulcerative colitis, chronic localized diverticulitis, and intestinal actinomycosis.

INCIDENCE

1. Age, Sex, and Race.—It is an essential part of the definition that the aetiology of Crohn's disease is unknown. We have found the age incidence similar to other workers (*Fig.* 221). The youngest patient in this series was aged 4 years and the oldest 69 years at the time of operation. There were 48 men (44 per cent) and 60 women (56 per cent). A similar slight preponderance of women was found by Cooke (1955) in Birmingham, whereas in the large American series reported by Ravdin and Johnston (1939), Warren and Sommers (1948), Crohn (1949), and van Patter and others (1954) there has been a slight preponderance of men.

Only 3 patients in this series were Jewish, the rest being Caucasian.

2. Relation to Pulmonary Tuberculosis.—In only 1 patient was there evidence of recent active pulmonary tuberculosis. This patient died soon after operation. The resected specimen of lower ileum showed the typical histological picture of Crohn's disease with pseudo-tuberculous follicles. In a number of resected specimens in which the histological changes of Crohn's disease were found in the bowel, there were calcified areas in associated lymph-nodes which were regarded, rightly or wrongly, as evidence of past tuberculous infection. In no specimen were acid-fast bacilli found, nor was there any caseation in the pseudo-tuberculous follicles when they were present.

3. Relation to Duodenal Ulcer.—Seven patients had radiological or pathological evidence of duodenal

ulceration either before or after treatment of their Crohn's disease. This represents 6·3 per cent of the series of 108 patients. During the period 1953–4 among 38,939 admissions to the Leeds General Infirmary there were 1383 patients in whom duodenal ulcer was the primary or secondary diagnosis. This represents 3·55 per cent. Although statistical analysis of these figures fails owing to the lack of similarity between the two populations, they suggest that

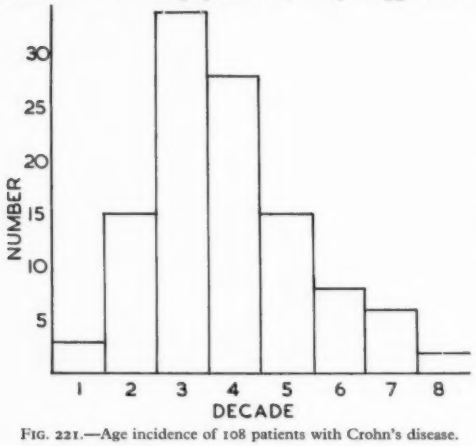

FIG. 221.—Age incidence of 108 patients with Crohn's disease.

duodenal ulcer is a not uncommon accompaniment of Crohn's disease. Cooke (1955) reported an even higher incidence of peptic ulceration (10 duodenal and 1 gastric ulcer in 90 patients with Crohn's disease), but van Patter and others (1954) found only 4 per cent of their 600 patients had concomitant duodenal ulcer, and stated that this figure was not higher than in the general population at the Mayo Clinic.

4. Relation to Ulcerative Colitis.—Surgical opinion is sharply divided on the relation of ulcerative colitis to Crohn's disease and ranges from that of Cattell, who considers that there is some connexion between the two diseases, to that of Brooke, who asserts that they are quite separate entities. In 7 patients a diagnosis of ulcerative colitis was entertained at some time during the course of the disease. These cases are summarized below:—

Case 1.—Female, aged 32 years in 1951. Diarrhœa since 1946. Thyroidectomy for toxic goitre, 1948. Sigmoidoscopic and radiological signs of ulcerative colitis involving whole colon, November, 1948; also fistula-in-ano. Laparotomy, March, 1949; Crohn's disease of terminal 2 in. of ileum, appendix, and proximal half of ascending colon; appendicectomy (histology showed a granulomatous lesion with follicles). Laparotomy and terminal ileostomy, March, 1951. Excision of rectum, September, 1951: extensive ulcerative colitis with pseudopolyps: histology showed a granulomatous condition with follicles. Died, November, 1951: autopsy showed Crohn's disease of the terminal ileum together with a diffuse ulcerative colitis.

Case 2.—Female, aged 35 years in 1953. Right hemicolectomy for subacute terminal ileal Crohn's disease, 1939. Diarrhœa, loss of weight, and an abdominal lump started in 1947. Laparotomy in 1948 showed enlarged mesenteric lymph-nodes. Fairly well until 1952, when she developed steatorrhœa with loss of weight, anæmia, and vitamin deficiencies. She was found to have a rectovaginal fistula and fistula-in-ano. Laparotomy in 1953 showed a thick vascular colon resembling ulcerative colitis: terminal ileostomy performed. She died in January, 1954. At autopsy the colon was not grossly diseased, but only 4 ft. of small bowel remained, and this was diseased.

Case 3.—Female, aged 18 years in 1955. Abdominal pain and diarrhœa since 1951. Barium enema, 1952, showed changes consistent with ulcerative colitis from cæcum to splenic flexure. She improved dramatically on cortisone, and remained well until January, 1955, when she had a relapse of abdominal pain without diarrhœa. Barium enema in June, 1955, showed an inflammatory lesion of the terminal ileum and right half of the colon. Fat-balance studies revealed an average daily excretion of 4·2 g. on a 50-g. fat diet. Right hemicolectomy, July, 1955, for Crohn's disease involving the terminal ileum, cæcum, and ascending and right half of transverse colon. Sections of the involved bowel (*see Fig.* 223) showed patchy ulceration alternating with hyperplastic mucosa and a non-specific inflammatory process with lymphoid hyperplasia extending through the bowel wall. Fifteen months later she was in excellent health, without diarrhœa.

Case 4.—Male, aged 38 years in 1955. Diarrhœa, ischiorectal abscesses, fistulæ-in-ano, low rectal stricture since 1947. Right hemicolectomy for Crohn's disease of terminal 8 in. of ileum, cæcum, and ascending colon with typical histology (*see Fig.* 224). He died four weeks later. Autopsy showed patchy mucosal ulceration of jejunum and upper ileum, and in the rectum and rectosigmoid.

Case 5.—Female, aged 26 years in 1956. Diarrhœa and loss of weight since October, 1954. Treated as ulcerative colitis (sigmoidoscopy showed mild mucosal changes) in July, 1955. In February, 1956, a barium meal was followed through and showed narrowing of the lower ileum. Fat balance (50 g. daily intake): she excreted an average of 8·5 g. daily (normal upper limit 5 g.). Resection of 16 in. of lower ileum, March, 1956, for Crohn's disease: the entire colon was vascular and œdematous, as in ulcerative colitis. The histological findings in this case are interesting (*see Fig.* 225). There was ulceration of the mucosa. Chronic granulation tissue with polymorphs, eosinophil cells, and plasma cells infiltrated the muscle coats and serosa and at one part of the serosa there was a small abscess. This reaction was regarded as non-specific, resembling ulcerative colitis. She suffered a recurrence of diarrhœa and loss of weight within a year after operation and is at present being treated medically for ulcerative colitis.*

Case 6.—This case is reported more fully in another connexion (*see Case* 22). Briefly, a woman of 22 years was operated on in 1951 for Crohn's disease of the terminal ileum. An ileotransverse colostomy was done and a biopsy showed pseudo-tuberculous follicles. Two years later the abdomen was re-opened as she had a profound intestinal deficiency syndrome. At that time the entire small bowel was found to be thickened and biopsy from jejunum and stomach suggested Crohn's disease. No operation was possible. Two years later she began to improve and had a remission lasting two years. Finally, in 1957, six years after the initial operation, she again became extremely ill; multiple perianal abscesses and fistulæ had developed with sigmoidoscopic appearances of severe ulcerative colitis. She is at present under treatment with ACTH and is improving.

Case 7.—This patient has not been included in the series as the existence of Crohn's disease has not been proved. She shows, however, great similarity to cases of

* Since this article was submitted for publication the patient has undergone a total colectomy. The histological changes are those of Crohn's disease.

Crohn's disease, particularly in the radiological features. Female, aged 16 years in 1954. Diarrhœa with blood and mucus in attacks since the age of 7 years. Severe attack with abdominal pain and wasting, 1954. Barium enema showed marked mucosal changes in ascending and transverse colon and a narrowed distorted terminal ileum (*see Fig.* 226). Sigmoidoscopy was normal. Ulcerative colitis was diagnosed and she was treated with ACTH with dramatic improvement. Relapse occurred in 1956, when a tender mass was palpable in the right iliac fossa. The findings were essentially the same and a fat-balance test showed an average daily fat excretion of 4·7 g. with a 50 g. daily intake. She again responded very well to cortisone.

The association between Crohn's disease and ulcerative colitis has been much discussed (Crohn, 1949). There are two forms of terminal ileitis secondary to ulcerative colitis which are not related to Crohn's disease (Counsell, 1956). These are first the 'backwash ileitis' (Crohn, 1949) which is probably due to incompetence of the ileocæcal valve (Inberg, 1953). In these cases there is no steatorrhœa or other clinical sign of small-bowel involvement and the condition recovers after colectomy, even if the diseased ileum is used for an ileostomy (J. C. Goligher, 1957; Counsell, 1956).

Although in these cases the terminal ileal wall may be considerably thickened, there is no encroachment on the lumen and the lesion shows little resemblance to Crohn's disease. Histologically the changes are very similar to those found in the colon, with ulceration, regeneration of a flat epithelium, crypt abscesses, and inflammatory cell infiltration.

Secondly, there is the more acute form of ileitis which sometimes goes on to hæmorrhage or perforation, which is confined to patients subjected to ileostomy with or without colectomy. This form is the result of 'ileostomy dysfunction' or obstruction (Warren and McKittrick, 1951) and is cured by relief of the dysfunction. It is rare after the mucosal suture method of ileostomy of Brooke (1954), which avoids stenosis at the ileostomy. It has not been seen after colectomy with ileorectal anastomosis for ulcerative colitis (Aylett, 1955). Grossly this type of ileitis presents with multiple small ulcers in the terminal ileum, with normal intervening mucosa. Histologically the ulcers resemble stercoral ulcers and the rest of the ileum is normal.

Apart from these two conditions, there is the controversial group of patients in whom sigmoidoscopic and radiological features of ulcerative colitis are accompanied by clinical manifestations (often in the form of steatorrhœa) and sometimes by radiological signs of a granulomatous enteritis closely resembling Crohn's disease. This condition has been called 'ileocolitis' by Brooke (1954), and he has emphasized the poor results of ileostomy with or without colectomy in these cases. There is, however, evidence that patients with classical Crohn's disease of the small bowel may develop a diffuse colitis, generally right-sided, resembling non-specific ulcerative colitis, and these patients have been considered to be primarily cases of Crohn's disease.

5. Relation to Psychological Disturbances.—No attempt has been made in this series to gain more than a superficial impression of the patients' mentality. It is not surprising that many of the patients who have suffered recurrences after operation and who have chronic diarrhœa and ill health show the sort of dependence seen in patients with ulcerative colitis. On the other hand, only one patient in the present series has spent any time in a mental hospital, and most of the patients who have been cured by operation appear conspicuously normal mentally. In Cooke's (1955) series of 90 patients there were 5 who were mentally deranged, and he reviews the literature on this aspect of aetiology.

6. Relation to Diet.—In many patients in this series symptoms were exacerbated by certain foods. The commonest offending foods were fats in all forms, and many patients with post-operative symptoms were improved by the omission of fats from the diet. No evidence was found of intolerance to milk, which van Patter and others (1954) found to be the commonest food idiosyncrasy in their 600 patients, but many patients stated that they were unable to eat vegetables, particularly of the cabbage family, without discomfort. No case of true food allergy was discovered.

FIG. 222.—Appearance at operation in a typical case of Crohn's disease.

PATHOLOGY

The gross appearance of a classical case of Crohn's disease is unmistakable (*Fig.* 222). The affected segment of bowel, usually 6–10 in. of terminal ileum, is thick and injected and juicy, with a granular serosa. The transition to apparently unaffected bowel is abrupt, although mucosal changes may be much more widespread than would appear from the look and feel of the unopened bowel. The mesentery is thickened and œdematous, so that ligation of its vessels may be hazardous. Sometimes concealed within the thickened mesentery and sometimes projecting as prominences from it, are enlarged fleshy, œdematous lymph-nodes. So-called 'tubercles' may be seen on the serosal surface of the bowel. These represent lymphoid collections.

This is the usual picture seen in 85–90 per cent of all patients with Crohn's disease. In the remaining 10–15 per cent there are unusual features. The lesions may be multiple, with normal bowel between—in this series 12 patients had multiple lesions. The lesion may be confined to the upper small intestine, leaving the terminal ileum normal. In this series there was 1 patient with recurrent Crohn's disease (proved by biopsy) of the stomach and entire small bowel, 2 with

Crohn's disease of the duodenum, and 11 with Crohn's disease of the jejunum or upper ileum.

Occasionally the lesions are confined to the colon, and it is in this group that the distinction from ulcerative colitis or localized diverticulitis may be so difficult. There were 6 patients in this series with lesions confined to the colon, and 1 further patient in whom the diagnosis of Crohn's disease was changed to diverticulitis after reviewing the histology. He has been excluded from the series.

In 20 patients an internal or *abdominal fistula* complicated the disease. The internal fistulæ were commonly ileo-ileal, ileocolic, and ileovesical, and the external fistulæ commonly followed appendicectomy or (in 3 patients) the discharge of a pelvic abscess per vaginam with the formation of an ileo-vaginal fistula. In addition to these, an associated *fistula-in-ano* was found in 7 patients. This often antedated the symptoms of Crohn's disease, sometimes by years. In 1 case microscopical sections of the fistula showed pseudo-tuberculous follicles, but in the remainder no characteristic histological changes were found. Except in 1 patient with an internal opening above the anorectal ring, the fistulæ were cured by a standard excision operation, whether or not the Crohn's lesion of the intestine was treated.

FIG. 223.—*Case* 3. Inflammatory lesion of terminal ileum and cæcum. This section shows the lesion in the cæcum which is indistinguishable from ulcerative colitis. Note the œdema and inflammatory-cell infiltration. (× 40.)

FIG. 224.—*Case* 4. Typical Crohn's disease without follicles from terminal ileum of a patient with ulcerative proctitis and rectal stricture. Note the goblet-cell increase, patchy mucosal ulceration, œdema, round-cell infiltration, and focal lymphocyte accumulations. (× 40.)

FIG. 225.—*Case* 5. A lesion of the lower ileum, clinically and grossly Crohn's disease but microscopically resembling ulcerative colitis. Note the mucosal atrophy, inflammatory-cell infiltration, lymphocyte accumulations, and lack of œdema. (× 48.)

The presence of *steatorrhœa* before operation is accepted by Cooke (1955) as evidence of a widespread small-bowel dysfunction, of which the obvious Crohn's lesion is but one part. This is an important concept and provides an explanation for the frequency of recurrence.

HISTOLOGY

In less than half of the patients in the present series was the Crohn's lesion resected. To add to the material available for histological study there were in addition 15 specimens previously not resected, removed at a subsequent operation for recurrent Crohn's disease. In all 58 specimens were resected, of which 9 are no longer available. The specimens from the remaining 49 patients have been re-examined histologically.

The histological changes have been well described by Hadfield (1939), Warren and Sommers (1948), and Rappaport, Burgoyne, and Smetana (1951). They may be summarized as patchy ulceration, which may be mucosal or deeper, lymphatic dilatation, lymphoid hyperplasia, round-cell infiltration (*Fig.* 224), and in one-third of the cases, tuberculoid follicles (*Figs.* 227, 228). Caseation is not found. Granulomatous changes may be found in draining lymph-nodes, but it is commoner to find only reactive sinus catarrh and follicular hyperplasia. Calcification was not

uncommon in the nodes and was taken to indicate previous tuberculous infection.

In some cases the histological diagnosis of Crohn's disease presents no difficulty, but there are three conditions which may easily be confused with it. They are ulcerative colitis, localized diverticulitis, and tuberculosis.

Ulcerative Colitis.—There were histological preparations available from 4 patients in whom a microscopical diagnosis of ulcerative colitis was strongly suggested, although the clinical history and gross appearances suggested Crohn's disease. Two of these patients have been discussed (*Cases* 3 and 5, *Figs.* 223 and 225). The other 2 case histories are summarized as follows:—

Case 8.—A man aged 29 years with one year's history of right-sided abdominal pain and diarrhœa. Barium-meal examination showed the 'string sign' of Kantor. At operation the ileum was normal, the cæcum and ascending and proximal half of transverse colon being grossly thickened. The left half of transverse colon was normal, and the descending colon showed a similar thickening. Subtotal colectomy with ileosigmoidostomy was done and the patient is now (five years later) in fair health, but has periodic attacks of abdominal pain, vomiting, and constipation. Sections of the involved bowel showed (*Fig.* 229) an appearance resembling colitis polyposa.

Case 9.—A woman aged 38 years had intermittent abdominal pain, flatulence, and vomiting for eighteen years. During the two years preceding operation the symptoms were more severe and were accompanied by

FIG. 226.—*Case* 6. A patient at present being treated for ulcerative colitis. Barium enema shows changes of ulcerative colitis in ascending and transverse colon, and narrowing and distortion of terminal ileum. Is this Crohn's disease?

FIG. 227.—A follicle in the submucosa of terminal ileum of a patient with Crohn's disease. There is some similarity to a tuberculous follicle and a striking resemblance to the follicles of sarcoidosis and chronic brucellosis. (× 88.)

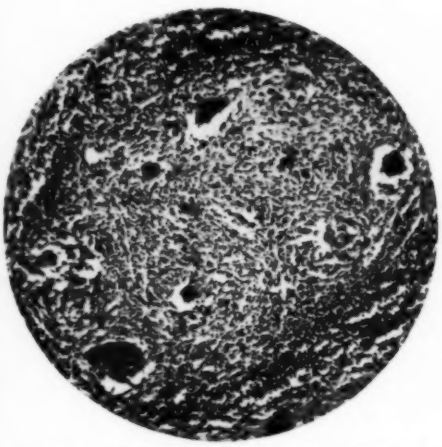

FIG. 228.—A follicle in the submucosa of ascending colon of a patient with Crohn's disease. The resemblance to a tuberculous follicle, apart from the lack of caseation, is striking. (× 88.)

FIG. 229.—*Case* 8. Inflammatory lesion of the ascending colon. The terminal ileum was normal and the lesion shows some resemblance to colitis polyposa. (× 17·6.)

diarrhœa. A mass was felt in the right iliac fossa and a barium enema showed a filling defect of the cæcum. At operation the terminal ileum was strictured and there was a short ileocæcal fistula. Right hemicolectomy was done and the patient is now (twelve years later) in good health. Sections of the lesion showed a non-specific inflammatory and ulcerative condition of the terminal ileum resembling ulcerative colitis.

Localized Diverticulitis.—One patient previously regarded as a case of Crohn's disease of the colon was reclassified as diverticulitis after a review of the histology, and has been omitted from the present series. His history is as follows:—

Case 10.—A man aged 70 years was admitted with complete colonic obstruction which responded to enemas. Five days later a large 'growth' in the sigmoid colon, with much fixity and peritoneal involvement, was resected. The patient is now (eighteen months later) in good health. The specimen showed marked thickening of the bowel wall over a distance of 8 cm., with polypoidal mucosal hypertrophy. In the subserosa was a broad band of chronic granulation tissue with giant cells. The lack of mucosal ulceration, the clinical picture, and the foreign-body giant cells support the diagnosis of diverticulitis.

Tuberculosis.—The distinction between Crohn's disease and hypertrophic ileocæcal tuberculosis is very fine and in this series the absence of acid-fast bacilli and caseation necrosis from the lesions and lymph-nodes, and the absence of pulmonary tuberculosis (except in 1 patient) have been held to support the non-tuberculous nature of the lesions. Anand (1956) reported 50 right hemicolectomies from Amritsar in India for hypertrophic ileocæcal tuberculosis. He found giant-cell follicles in the intestinal wall in 38 of these patients. In only 5 cases was there caseation in the follicles. On the other hand, the regional lymph-nodes showed follicles with caseation in all cases, and he was able to culture tubercle bacilli from intestinal scrapings or lymph-nodes in 25 of 39 patients, none of whom showed any lung lesion.

FIG. 230.—*Case* 11. A giant-cell follicle from the terminal ileum showing well-marked caseation. This is regarded as tuberculous and this case is excluded from the series. (× 60.)

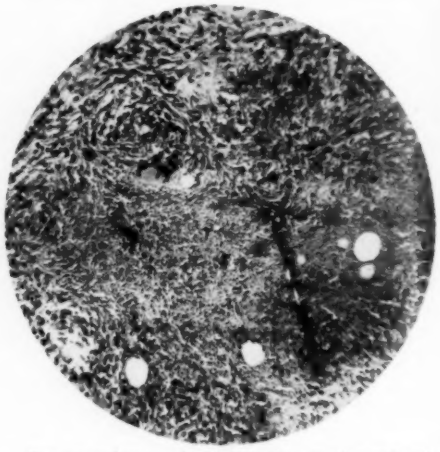

FIG. 231.—*Case* 12. A follicle in the ascending colon of a woman whose disease spared the terminal ileum. The presence of caseation necrosis in this and other follicles proclaims tuberculosis and this case is excluded from the series. (× 88.)

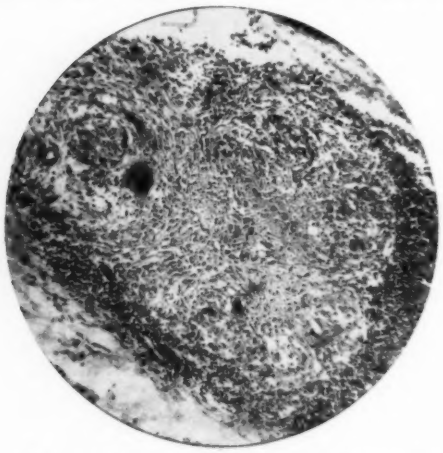

FIG. 232.—*Case* 13. A follicle in the submucosa of the ascending colon from a patient whose lesion clinically and grossly resembled Crohn's disease. The small amount of caseation necrosis raises the strong possibility of tuberculosis and this case is excluded from the series. (× 88.)

Three patients previously thought to have Crohn's disease have been reclassified as intestinal tuberculosis on the basis of small amounts of caseation in follicles in the intestinal wall or lymph-nodes. These 3 cases are summarized below. It will be seen that 2 (*Cases* 11, 12) differ from the classical picture of Crohn's disease, whereas the third (*Case* 13) was considered to be a typical example of Crohn's disease until the discovery of caseation in giant-cell follicles.

Case 11.—A man aged 33 years was admitted with a history of three years' recurrent abdominal colic and indigestion. He had lost 14 lb. in weight and was tender in the right iliac fossa. At laparotomy the terminal 2 in. of ileum and the adjacent part of cæcum were thickened, œdematous, and congested. Right hemicolectomy was done and he made a good recovery, only to die 2½ years later of pulmonary tuberculosis. The specimen showed three ulcers in the terminal ileum, placed longitudinally.

The lowest one involved the ileocæcal valve. There was no marked thickening of bowel wall or narrowing of the lumen. Histologically, there were chronic inflammatory changes and giant-cell follicles showing well-marked caseation (*Fig.* 230). Similar changes were found in lymph-nodes.

Case 12.—A woman aged 74 years was successfully treated with vitamin B_{12} for a macrocytic anæmia four

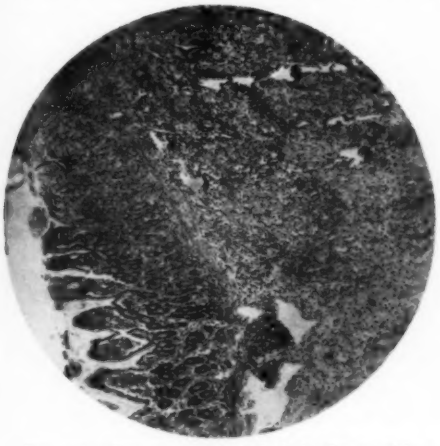

FIG. 233.—*Case* 14. Typical Crohn's disease without follicles in a woman of 28 with two weeks' history of abdominal pain. Note the patchy mucosal ulceration, œdema, round-cell infiltration, and aggregations of lymphocytes. (× 40.)

years before right hemicolectomy. Two months before hemicolectomy she became increasingly tired and breathless, and lost appetite and weight. She showed an iron-deficiency anæmia and occult blood was present in the stools. A barium-enema examination showed a filling defect of the cæcum and a diagnosis of carcinoma of the cæcum was made. At operation the cæcum and ascending colon were thickened and firm. Right hemicolectomy was done and she died a month later. The specimen showed a relatively normal terminal ileum, apart from several small polyps, but irregular areas of confluent ulceration in the colon with œdema of non-ulcerated mucosa. In the ileocæcal angle were slightly enlarged lymph-nodes. There was no stenosis of the bowel. Histologically a chronic inflammatory reaction was found with scattered giant-cell follicles showing caseation necrosis (*Fig.* 231). No acid-fast bacilli were found; no signs of pulmonary tuberculosis at autopsy. Lymph-nodes showed only reactive hyperplasia.

Case 13.—A woman aged 43 years with a two years' history of abdominal pain, vomiting, diarrhœa, and borborygmi in attacks, presented with a tender mass in the right iliac fossa. Right hemicolectomy was done. The patient is in excellent health two years later. The specimen showed thickening and stenosis in terminal ileum and cæcum, with thick œdematous mesentery and enlarged lymph-nodes. It was thought to be characteristic of Crohn's disease. Histologically, however (*Fig.* 232), some of the giant-cell follicles in intestine and lymph-nodes showed slight caseation necrosis. No acid-fast bacilli were found.

STAGES OF THE DISEASE

The grading of cases of Crohn's disease on a pathological basis is unsatisfactory and I have found it unprofitable to attempt to follow Crohn, Ginzberg, and Oppenheimer (1932) in dividing these cases into acute, ulcerative, stenotic, and stage of persistent fistula.

Instead it has been found fruitful, from the point of view of prognosis, to divide this series into three clinical groups, based on the length of history. These are:—

Acute Crohn's disease: history less than 1 month.

FIG. 234.—*Case* 15. Typical Crohn's disease in the terminal ileum from a woman aged 53 years with a total history of no more than three weeks. (× 40.)

Subacute Crohn's disease: history 1 month to 2 years.

Chronic Crohn's disease: history longer than 2 years.

I have had certain misgivings about the diagnosis of the disease in the acute group, most of which were discovered at laparotomy undertaken for appendicectomy. Usually nothing was done or the appendix was removed. In 2 cases, however, the involved bowel was removed and showed the histological changes of Crohn's disease. Their histories are summarized below:—

Case 14.—A woman aged 28 years was admitted with a two weeks' history of abdominal pain. She was tender and rigid in the right iliac fossa and a diagnosis of acute appendicitis was made. At operation the appendix, cæcum, and terminal ileum were normal. Twelve inches proximal to the ileocæcal valve was a 10-in. segment of ileum which was injected, thick, and succulent. The mesentery and lymph-nodes were enlarged. The involved ileum was resected and the patient is now (six years later) in excellent health. The specimen showed gross œdematous thickening of all coats of the bowel, with narrowing of the lumen. Histologically (*Fig.* 233) the appearance was typical of Crohn's disease without follicles.

Case 15.—A woman aged 53 years was seen with a tender mobile mass in the right iliac fossa. Her history dated back no further than three weeks, during which time she had felt off colour and had had pain in the right iliac fossa. At operation the terminal 5 in. of ileum was thick, red, and succulent. The mesentery was œdematous and there were enlarged lymph-nodes in the ileocæcal angle. Right hemicolectomy was done and the patient is now (three years later) in excellent health. The specimen

showed typical macroscopical and microscopical changes of Crohn's disease (*Fig.* 234).

In addition to these 2 cases, a third patient with a short history was found at operation to have a Crohn's lesion in the terminal ileum. Ileotransverse colostomy was done and the patient suffered an early recurrence, for which the involved bowel was removed six months later. This specimen also showed histological changes of Crohn's disease.

There seems little doubt, therefore, that the finding at operation of a hyperæmic, thick, œdematous segment of bowel with a granular serosa often covered by a fibrinous exudate, a thick succulent mesentery, and enlarged regional lymph-nodes, denotes Crohn's disease even if the history is short.

SYMPTOMS AND SIGNS

Acute Crohn's Disease (*Table II*).—Most of these 37 patients were operated on with a provisional diagnosis of acute appendicitis. Their history

Table II.—Symptoms in 108 Patients with Crohn's Disease

Pain	Acute	100%
	Subacute	97%
	Chronic	89%
Vomiting	Acute	26%
	Subacute	34%
	Chronic	36%
Diarrhœa	Acute	16%
	Subacute	63%
	Chronic	72%
Weight loss	Acute	
	Subacute	37 %
	Chronic	57%

was seldom of more than a few days' duration, and their outstanding complaint was pain (in all cases), sometimes accompanied by vomiting. Diarrhœa was not common; it was reported in only 6 patients in this series (16 per cent). Pyrexia of 99°–100° F. was usual and tenderness in the right iliac fossa was almost invariably present. In only 4 patients (10 per cent) was a lump present, in each case in the right iliac fossa and in each case diagnosed before operation as an appendix abscess. In no patient was there an abdominal or anal fistula. In none of these patients are there records of fæcal fat-balance estimations before operation, and in only 2 was a blood-count done (in both there was a mild iron-deficiency anæmia).

It is obvious that the diagnosis of acute appendicitis was very reasonable in nearly all these patients. At laparotomy the gross findings were typical of the acute stage of Crohn's disease, as already discussed under 'Pathology'.

Subacute Crohn's Disease.—Abdominal pain was again the most common symptom in those 39 patients whose history was of 1 month to 2 years' duration. The pain was usually in the form of ill-defined colic which sometimes fairly closely followed eating, was associated with abdominal rumblings, and sometimes terminated by diarrhœa. When this syndrome was displayed by a young person the clinical diagnosis of Crohn's disease was strongly suggested. In 18 patients (46 per cent) a lump was present in the right iliac fossa and made the clinical diagnosis complete. It was confirmed by radiography in 14 patients (38 per cent).

Sometimes the clinical picture was much less clear-cut than this and might be dominated by diarrhœa (in 22 patients, or 63 per cent), loss of weight (13 patients, 36 per cent), or ill-defined malaise. One patient presented with severe bowel hæmorrhage and no other symptoms.

Three patients had a fistula-in-ano; in 2 this preceded the symptoms of Crohn's disease by 2–4 years, in 1 patient it accompanied a second recurrence of Crohn's disease 14 years after the first operation and 6 years after the second operation.

Chronic Crohn's Disease.—There were 30 patients whose history was longer than 2 years. In most of them the history was dominated by intermittent diarrhœa, with mild abdominal pain of colicky type, borborygmi, loss of weight, anæmia, and a lack of enjoyment of life which encouraged a diagnosis of psychoneurosis in many of them. This question of the relation of mental disturbances to the disease has been discussed under 'Aetiology'. There seems little doubt that in many patients the depression and lassitude have been engendered by their lesion and not vice versa.

Only a quarter of these patients were found to have a lump, which was usually in the right iliac fossa. Four patients had a fistula-in-ano, in each case accompanying the other symptoms of Crohn's disease.

Table III.—Clinical Differentiation between Crohn's Disease and Ulcerative Colitis

	Crohn's Disease	Ulcerative Colitis
Age	Young adults but no age immune	Young adults but no age immune
Sex	Commoner in women	Commoner in women
Mental influences	Present	Present
Diarrhœa	Common	Nearly always
Ileal involvement	Nearly always	Not uncommon
Blood in stool	Not uncommon	Common
Mucus and pus in stool	Uncommon	Common
Loss of weight	Common	Common
Intestinal obstruction	Common	Not found
Steatorrhœa	Common	Not found
Iritis, arthritis	Uncommon	Not uncommon
Malignant change	Not found	Not uncommon
Fistula-in-ano	Not uncommon	Not uncommon
Perforation and fistula	Not uncommon	Uncommon
Recurrence after resection	Common	Not found

Anæmia was not uncommon and was usually of iron-deficiency type. Frank bowel hæmorrhage was rare, but occult blood was commonly found in the stool.

Diagnosis.—The diagnosis of Crohn's disease in the subacute and chronic group is suggested by the history. In the acute group it can seldom be made before operation, a diagnosis of acute appendicitis usually being very reasonably made.

Conditions to be differentiated from Crohn's disease are idiopathic steatorrhœa and the sprue syndrome; intestinal lipodystrophy or Whipple's disease (Wang, Janowitz, and Adlersberg, 1956); ulcerative colitis (*Table III*); carcinoma of the right colon; benign and neoplastic strictures of the small intestine; and finally psychoneurosis.

The radiological diagnosis of Crohn's disease may be easy or, on the other hand, it may be impossible to

distinguish this condition from other inflammatory and malignant conditions in the ileocæcal region. A barium-enema examination is usually more reliable than a barium meal and follow-through. The classical 'string sign' of Kantor (1934) implies a fairly long

FIG. 235.—A typical stricture of the terminal ileum in a case of Crohn's disease.

irregular narrowing of the terminal ileum (*Fig.* 235), usually with some delay and dilatation of the ileum above. A less common finding is a short stricture of the terminal ileum with considerable irregular dilatation above (*Fig.* 236). The margins of this dilated segment of ileum may be ragged from ulceration, or may show a 'cobblestone' appearance from œdematous thickening of the wall (*Fig.* 237). In recurrent cases dilatation alone may be found at the site of the disease.

In every case the patient should be admitted for a three- or five-day fat-balance test. On a daily fat intake of 50 g. about half of the patients will excrete more than 5 g. of total fatty acids per 24 hours (i.e., less than 90 per cent absorption). This test is now being applied routinely in patients with Crohn's disease, but results are available for only 5 patients, of whom 2 showed steatorrhœa and 3 no steatorrhœa before operation. Cooke (1955) found that 12 of 21 patients had steatorrhœa before operation. This test is likely to be valuable in assessing the prognosis in individual patients, those with steatorrhœa being more liable to recurrence than those without (Cooke, 1955).

Examination of the blood may show a mild iron-deficiency anæmia, and polymorphonuclear leucocytosis accompanies acute exacerbations. In only 1 patient was a macrocytic blood-picture found before operation, although such a picture is not uncommon as an indication of recurrent disease.

In the more severe cases of Crohn's disease the factors of chronic intestinal obstruction, diarrhœa, steatorrhœa, inflammation, and perhaps external fistula, may combine to produce florid malnutrition. This shows itself in gross wasting, finger clubbing, hypoproteinæmia, potassium depletion, vitamin deficiencies, and osteomalacia. There have been several examples of such a syndrome in this series, but only 1 patient with biochemical changes of osteomalacia (a man with recurrent Crohn's disease).

FIG. 236.—Short stricture of terminal ileum with ragged dilatation above, from a case of Crohn's disease.

FIG. 237.—Cobblestone appearance of mucosa of terminal ileum in a case of Crohn's disease.

RESULTS OF TREATMENT

All except 3 patients in this series had an operation. In 2 of these the diagnosis was made at autopsy in patients admitted moribund with intestinal obstruction. The third patient has only recently been studied and is being treated medically.

Of the remaining 105 patients, in 46 the lesion was resected, in 13 by-passed, and in 46 the lesion itself was not treated, either an appendicectomy or

a simple laparotomy being done. The term 'by-pass' is used to include short-circuiting operations such as ileocolostomy, and also short-circuiting operations with total deflection of the fæcal stream by division of the bowel and permanent delivery of the defunctioned part as a non-functioning distal ileostomy.

Half of these patients (52) have been followed for between 5 and 18 years, and it is in this group that the incidence of recurrence is assessed (*Tables IV, IVa, V, Va, VI, VIa*).

Table IV.—17 Patients with Acute Crohn's Disease Followed More Than 5 Years

	Total	Grade			Recurrence	
		A	B	C	Number	Per cent
Resection	1	1	—	—	—	—
By-pass	2	1	—	—	1	—
Laparotomy or appendicectomy	14	11	1	1	1	—
Total	17	13	1	1	2	12

Table V.—18 Patients with Subacute Crohn's Disease Followed More Than 5 Years

	Total	Grade			Recurrence	
		A	B	C	Number	Per cent
Resection	14	3	7	2	2	—
Laparotomy or appendicectomy	4	2	—	—	2	—
Total	18	5	7	2	4	22

Table VI.—17 Patients with Chronic Crohn's Disease Followed More Than 5 Years

	Total	Grade			Recurrence	
		A	B	C	Number	Per cent
Resection	9	—	1	2	6	—
By-pass	6	2	—	—	4	—
Laparotomy or appendicectomy	2	1	—	—	1	—
Total	17	3	1	2	11	65

For example Homb (1946) followed 28 patients in whom he found acute ileitis at laparotomy from 1 year to 7½ years and was unable to show clinically or radiographically any evidence of progression to the chronic form of the disease.

Six patients with acute Crohn's disease treated by laparotomy alone or with appendicectomy have been examined radiographically by barium meal or enema since operation. In 5 of them no trace of the Crohn's lesion was found. In the sixth patient there was an

Table IVa.—11 Patients with Acute Crohn's Disease Followed More Than 10 Years

	Total	Grade			Recurrence	
		A	B	C	Number	Per cent
By-pass	1	1	—	—	—	—
Laparotomy or appendicectomy	11	9	1	1	—	—
Total	12	10	1	1	—	—

Table Va.—10 Patients with Subacute Crohn's Disease Followed More Than 10 Years

	Total	Grade			Recurrence	
		A	B	C	Number	Per cent
Resection	7	1	4	1	1	—
Laparotomy or appendicectomy	3	2	—	—	1	—
Total	10	3	4	1	2	20

Table VIa.—8 Patients with Chronic Crohn's Disease Followed More Than 10 Years

	Total	Grade			Recurrence	
		A	B	C	Number	Per cent
Resection	4	—	—	—	4	—
By-pass	3	2	—	—	1	—
Laparotomy or appendicectomy	1	—	—	—	1	—
Total	8	2	—	—	6	75

Grade A: No symptoms.
Grade B: Mild symptoms, not interfering with work or enjoyment of life.
Grade C: More severe symptoms, restricting activities.

Acute Crohn's Disease.—Seventeen patients whose pre-operative history was shorter than 1 month have been followed more than five years (*Table IV*). Thirteen of these patients have had no further trouble and are at present symptom-free. Two patients have gastro-intestinal symptoms (mild diarrhœa, occasional pain, borborygmi, etc.) which do not incapacitate them. Two patients (12 per cent) have suffered recurrence of their disease necessitating further treatment.

This satisfactory outcome appears to be permanent (*Table IVa*) and has been found by other workers.

area of irregular dilatation and constriction in the terminal ileum, with some hold-up of the barium meal above it (*Fig.* 238). His history is given below:—

Case 16.—A man aged 37 years was operated on in 1948 for abdominal pain of two weeks' duration. A pre-operative diagnosis of acute appendicitis was made, but at laparotomy the findings were those of acute Crohn's disease of the terminal ileum. The appendix was removed and he remained well for just over a year. For the past 7 years, however, he has had intermittent abdominal pain of dyspeptic type, unaccompanied by diarrhœa or vomiting. He also has bilateral bronchiectasis. His weight is maintained and there are no abnormal signs on abdominal

examination. Barium-meal examination strongly suggests recurrent Crohn's disease.

Subacute Crohn's Disease.—Eighteen patients whose pre-operative history was longer than 1 month, but shorter than 2 years, have been followed more than 5 years (*Table V*). In 14 patients the lesion was resected; in 4 it was left alone. There were more recurrences than in the acute group (4, or 22 per cent), and more of the patients had complaints

FIG. 238.—*Case* 16. Irregular dilatation and constriction in the terminal ileum. An area of Crohn's disease had been found at laparotomy for acute symptoms 8 years previously. The patient now has intermittent abdominal pain, and must be regarded as having recurrent disease.

of diarrhœa, occasional abdominal pain, wind, and necessity for avoidance of certain foods, especially fats. The overall picture, however, is fairly bright and the incidence of recurrence not unduly discouraging.

Chronic Crohn's Disease.—Seventeen patients whose pre-operative history was longer than 2 years have been followed more than 5 years since operation (*Table VI*). In this group, whether the lesion was resected, by-passed, or left alone, there was a high incidence of recurrence, amounting in aggregate to 11, or 65 per cent. Only 3 of the group of 17 are now in perfect health, and 2 of these had their operation more than 10 years ago.

FACTORS CONTRIBUTING TO RECURRENCES

Why are some patients cured by operation and others not? In an attempt to answer this question some factors have been analysed for a group of 29 recurrent cases, and compared with the total group. This group includes all recurrent cases, whether or not the initial operation was more than 5 years ago. There are more patients, therefore, than is indicated in *Tables IV*, *V*, and *VI*.

Sex.—There were 20 females and 9 males amongst the patients whose disease recurred. This preponderance of females (69 per cent) is greater than in the whole series (56 per cent).

Age.—Thirteen patients were in the third decade at the time of the first operation, 11 in the fourth, 3 in the fifth, and 1 each in the sixth and seventh decades. This is not greatly different from the age distribution in the whole series, except that in no patient under the age of 20 did a recurrence subsequently develop.

Length of Follow-up.—In 20 patients the symptoms of recurrence commenced within a year of the primary operation. In 6 the symptoms came on after one to five years, and in 3 after five to eight years. A patient remaining well for five years after operation has only a small chance of subsequent recurrence.

Extent of Bowel Resection.—Van Patter and others (1954) found a recurrence rate of 63 per cent when less than 50 cm. of bowel was resected, and one of 93 per cent when more than 80 cm. of bowel was resected. No figures can be given for the present series because in many cases the exact length of resected bowel was not indicated, but in general the same relation was found. This probably means only that the more extensive the initial disease, the greater the chance of recurrence.

Pre-operative Diarrhœa plus Weight Loss.—Cooke (1955) gives the results of operation in 21 patients whose fæcal fats were estimated before operation. In 9 there was no steatorrhœa, and only 1 patient has developed a recurrence. In 12 steatorrhœa was present, and 7 have developed recurrences. Figures for fæcal fat estimations before operation in the early cases in this series are lacking, and diarrhœa together with loss of weight have been taken as pointers towards steatorrhœa. It was found that 12 patients with this combination before operation developed recurrences, whereas only 2 have been followed five years without recurrence. Pre-operative steatorrhœa almost certainly means widespread disease and lessens the chances of cure.

DIAGNOSIS OF RECURRENT CROHN'S DISEASE

The absolute criterion of recurrence of Crohn's disease is the histological demonstration of the changes at subsequent operation or autopsy. Clinically, however, recurrence can be reasonably assumed in the presence of the following symptoms or signs :—

1. Diarrhœa.—Mild diarrhœa is very commonly found after resection for Crohn's disease (it is probably commoner after right hemicolectomy for this disease than for carcinoma of the ascending colon). In itself it may mean nothing and may be permanent without deterioration of health. For example:—

Case 17.—A woman aged 38 years had a right hemicolectomy in April, 1944, for histologically proved Crohn's disease of the terminal ileum causing three months' indigestion, loss of appetite, and diarrhœa, and a lump in the right iliac fossa. Ever since operation she has had her bowels open four or five times daily, but has come to accept this as normal and is not distressed by it. At present, 12 years after operation, her weight is normal, her general health excellent, and there are no signs of abdominal disease.

Diarrhœa of this kind, not signifying active disease, is often precipitated by eating certain things, particularly fatty foods and fruit. It is not related to the extent of resection and may be found after resection of the ileum alone.

On the other hand, severe or increasing diarrhœa may be the first symptom of recurrent disease. It is usually accompanied by other symptoms like loss of weight and appetite, abdominal pain, and borborygmi. It may arise as a result of diffuse ileal disease (in which case it is usually accompanied by steatorrhœa), or as a result of an ileal stricture.

2. Steatorrhœa.—In patients with recurrent disease this is a very common finding. It is usually, but not always, accompanied by severe diarrhœa, the bowels moving more than six times daily. In only 10 of the 29 patients with recurrent disease was fæcal fat estimated. In every case the output was abnormally high.

Whether the converse is true or not is more uncertain. Does the presence of steatorrhœa in a patient who has been operated on for Crohn's disease always mean recurrence? There are two other possible mechanisms:—

a. It might be the expression of a very extensive resection. This has not usually in practice been found to be the case. Some of our patients are without steatorrhœa after very extensive resections, whereas others may have steatorrhœa after a more limited resection or a short-circuiting operation. Furthermore, a patient may recover normally from an operation for Crohn's disease and the fæcal fats may be normal and only become abnormal when other symptoms of recurrence appear. Finally, steatorrhœa, like the other 'intestinal deficiency' syndromes (hypoproteinæmia, loss of weight, vitamin deficiencies, anæmia) may respond to treatment and certainly improves with spontaneous remissions in the disease. In this series, however, it has been found that the more extensive the resection, the greater, on the whole, the chance of post-operative intestinal deficiency. In fact, these symptoms probably arise as a result of a combination of recurrent disease and an extensive resection.

b. It might be the expression of the so-called 'blind-loop syndrome'. The association between an intestinal cul-de-sac and vitamin B_{12} deficiency has been reviewed by Cameron, Watson, and Witts (1949). That a similarly disordered anatomy may be responsible for steatorrhœa as well is shown by Naish and Capper (1953), who report 5 such cases, in 1 of which the steatorrhœa was cured by abolition of the cul-de-sac. It might be assumed that steatorrhœa following a short-circuiting operation for Crohn's disease is the expression of the disordered anatomy rather than recurrent disease.

Eight recurrences following a by-pass operation have been studied. In five of them a second operation was done and active Crohn's disease demonstrated histologically. In the remaining 3 cases, however, an intestinal cul-de-sac effect may be responsible for their symptoms. These case histories are summarized below:—

Case 18.—A woman aged 26 years with a history of diarrhœa since the age of 7 years, and more recently loss of weight and attacks of abdominal pain and distension culminating in vomiting, was found to have steatorrhœa (total fat 40·2 per cent of dry weight) and a subacute small-bowel obstruction on radiography. At operation, in November, 1949, the jejunum was found to be distended above four strictures of the ileum. One stricture was excised for histology (which showed Crohn's disease) and a jejuno-transverse colostomy with exclusion of the diseased ileum was done. The patient was very well for 2 years, gaining weight and having only two or three motions daily. In 1951 she relapsed, having frequent offensive stools, vomiting, and attacks of abdominal pain. She lost weight. In 1954 she was re-admitted, found to have steatorrhœa (total fats 54·8 per cent of dry weight) and mild anæmia (R.B.C. 4·02 million, hæmoglobin 81 per cent, colour index 1). She was treated with oxytetracycline with improvement in the diarrhœa.

She soon relapsed and was again in hospital in May, 1955, when she was again anæmic (R.B.C. 3·59 million, hæmoglobin 67 per cent, colour index 0·9). On this occasion a barium-meal examination showed a large atonic stomach with considerable 5-hr. residue, and a distended loop of small bowel. She was last seen in August, 1956, 7 years after her operation. She was taking iron regularly, vomited from time to time, and the bowels acted 3-6 times daily. She rated her health as fair. Unfortunately she will not accept further investigation, and it is difficult to say whether her symptoms are the result of recurrence of Crohn's disease or of the presence of a long blind loop of ileum.

Case 19.—A man aged 61 years was operated on in April, 1951, for extensive Crohn's disease of terminal ileum and cæcum. An ileotransverse colostomy was done and the patient improved considerably. He was, however, never free of diarrhœa, which by June, 1956, when he was last seen, amounted to up to twenty motions daily. He had steatorrhœa (total fats 58 per cent of dry weight) and anæmia (R.B.C. 3·3 million, hæmoglobin 62 per cent, colour index 0·93). He failed to attend for X-ray examination of the intestine.

Case 20.—A man aged 37 years with a long history of abdominal pain and diarrhœa was operated on in March, 1943. Crohn's disease of the terminal ileum was found, resected, and continuity restored by ileotransverse colostomy leaving a 20-cm. blind loop of ascending colon. His diarrhœa did not settle after operation, the bowels being opened 3–14 times daily. In 1954, eleven years after operation, the blind loop was resected. It showed no histological evidence of Crohn's disease, but his symptoms have not improved. His weight remains below normal, he is always tired, he has severe diarrhœa, borborygmi, and occasional abdominal pain. In June, 1956, he was not anæmic (R.B.C. 4·8 million, hæmoglobin 99 per cent, colour index 1·0). Barium-meal and enema examination showed the anastomosis and the small and large intestines. There were no radiological signs of Crohn's disease. In this case it was thought that the symptoms would be cured by resection of the cul-de-sac. That hope has not been fulfilled and there remains the possibility that he has recurrent Crohn's disease not showing itself on radiographs.

3. Anæmia.—A hæmoglobin content of less than 10 g. per 100 ml. was a very common sign of recurrence. It was found in 12 of the 29 patients with recurrent disease. In 3 the anæmia was macrocytic, with a colour index of more than 1. In each there was gross steatorrhœa. One patient is now in reasonable health and has a normal blood-count. She has been having liver extract and later vitamin B_{12} and an iron preparation for eleven years. One patient is in poor health after resection of his second recurrence, but now (three years after the discovery of a macrocytic anæmia) has a secondary anæmia with a colour index of 0·9. The third patient died and her blood-picture remained macrocytic until her death.

In 7 patients the anæmia was secondary or iron-deficient in type. In 1 it later became macrocytic, in 2 it has responded completely to oral administration of iron, and in the remaining 4 it is unchanged over a period of months or years.

In the remaining 2 patients only a low hæmoglobin estimation is available. One patient died after operation for a recurrence, and the other is now in good health.

4. Hypoproteinæmia.—This was discovered in 3 patients, each of whom was grossly œdematous. With treatment this deficiency has considerably improved (with disappearance of the œdema) in 1 patient. A second patient is at present under treatment without improvement in the serum-proteins, and the remaining patient died after operation for a second recurrence.

5. Osteomalacia.—No case of frank osteomalacia secondary to steatorrhœa in recurrent Crohn's disease has been found, but 1 patient shows a consistently low serum-calcium level and a calcium infusion test (Nordin and Fraser, 1956) shows an osteomalacic result. This patient's history is as follows:—

Case 21.—A man aged 26 years was operated on for subacute Crohn's disease of 9–12 months' duration in 1953. The affected segment of small bowel was resected and the patient was well for 18 months, although he had mild diarrhœa. More severe diarrhœa (twice or three times daily) and loss of weight then started and six months later he noticed swelling of the ankles. When he was admitted to Leeds General Infirmary in 1956 he was found to be anæmic (hæmoglobin 81 per cent, R.B.C. 4·3 million, colour index 0·9); he showed clubbing and mild general œdema. The serum-proteins were: albumin 2·2 per cent, globulin 2·4 per cent, total 4·6 per cent. He had severe steatorrhœa (39 g. total fatty acids excreted in 3 days on a 50-g. daily fat intake). Serum-calcium was 8·1 mg. per 100 ml., phosphorus 3·8 mg. per 100 ml., and alkaline phosphatase 9 units per 100 ml. A calcium infusion test showed that only 5 per cent of an intravenously administered dose of 705 mg. of calcium chloride was excreted over a period of 12 hr. Radiography of lumbar spine and pelvis failed to show osteoporosis. Examination of the intestine by barium meal followed through showed clumping in the middle part of the small bowel. There was no evidence of obstruction.

On a high-protein, low-fat diet supplemented by oral calcium gluconate and calciferol the patient improved symptomatically, but six months later his blood chemistry remained unchanged. He is now under treatment with prednisone and is improving considerably.

6. Intestinal Obstruction.—In 6 patients recurrence of Crohn's disease was shown by complete or partial intestinal obstruction. In each case the recurrence was demonstrated and dealt with at a subsequent operation.

7. Fistula.—In 5 patients an abdominal fistula and in 1 patient each, an anal, a rectovaginal, and an ileovesical fistula led to the diagnosis of recurrent Crohn's disease.

8. X-ray Changes only.—Two patients in good health have been classed as recurrences on the basis of radiological evidence of abnormality in the terminal small bowel only. Whether this is justified, or whether the changes represent only completely healed disease, is debatable. These patients will be carefully followed up, since it is the opinion of van Patter and others (1954) that radiological changes may precede clinical evidence of recurrence.

Further Outlook after Recurrence.—Of the 29 patients with recurrent disease, 7 are dead and 7 are in poor health with severe symptoms. Eight are in fair health, but have constant symptoms which interfere with their work or their enjoyment of life. Only 7 can be described as reasonably or very good results, with only minor or occasional complaints.

Of 8 patients with a proved second recurrence (after operation on the primary disease and the first recurrence), 5 were again operated on, of whom 2 died after operation and 2 are unimproved; 1 is improved. Three patients were not subjected to a third operation; of these 1 is dead of Crohn's disease, 1 is unimproved, and 1 is improved.

TREATMENT OF CROHN'S DISEASE

It is perhaps superfluous to emphasize the role of conservatism in the treatment of this disease. The appallingly high recurrence rate after surgery for the chronic disease, and the fact that many patients are well several years after a laparotomy alone for the more acute forms of the disease, should discourage too eager a resort to surgery. The fact remains, however, that many patients with intestinal obstruction, fistula, and other mechanical effects of Crohn's disease have been greatly benefited by surgery.

The basis of the non-surgical treatment, as for ulcerative colitis, should be attention to the general health, correction of anæmia, and the provision of vitamins and a nourishing diet. Many patients are benefited by the reduction of fats in the diet. In some cases intolerance of particular items of food is found. This applies particularly to fruit and vegetables.

More specific measures include abdominal irradiation and cortisone (or ACTH). The results of abdominal high-voltage X-irradiation are doubtful. Only 1 patient in the present series has been treated in this way, for recurrent disease. The patient came to further operation without incurring any definite benefit from the irradiation. Opinions differ on the value of this form of treatment, but the consensus of opinion seems to be (van Patter and others, 1954) that some improvement is to be expected in most cases, although the majority will come to surgery sooner or later.

The role of corticoids in the treatment of Crohn's disease is even more controversial and no planned clinical trial has, to my knowledge, been carried out. Four patients in the present series have been treated with cortisone, 2 for primary and 2 for recurrent disease. In each case temporary improvement was produced, but each one has subsequently relapsed and the two primary cases have come to surgery.

Surgery.—There is no evidence from the present series of the superiority of either a resection or a short-circuiting operation. The length of bowel to be removed or by-passed will of course depend on the conditions found at operation, but it seems reasonable to limit the resection to the grossly diseased portions of bowel. It is not possible by a more extensive resection to 'remove all the disease', and it may be possible to aggravate a subsequent deficiency syndrome by such means. One patient who came to autopsy after three operations for Crohn's disease, and who died with a very severe intestinal deficiency, was found to have only 4 ft. of small intestine left, and that diseased. This case has previously been mentioned (*see Case* 2).

The treatment of recurrent disease should be on the same lines as that of the primary disease, with an

even stronger bias towards conservatism. The role of corticoids in the treatment of the deficiency syndromes deserves special mention. An occasional patient will make a remarkable temporary recovery, as in the following case:—

Case 22.—A woman aged 22 years was operated on in 1951 for subacute Crohn's disease causing diarrhœa and weight loss over a period of six months. The disease was found in the terminal ileum, which was by-passed by an ileotransverse colostomy. A biopsy of the diseased area showed a granulomatous lesion with pseudo-tuberculous follicles. She did not improve following this operation and a year later was re-admitted with persistent diarrhœa, emaciation, and gross œdema. Her hæmoglobin was 83 per cent (R.B.C. 4·0 million), fæcal fats were 54·4 per cent of fæcal dried weight, and plasma-proteins were 2·8 per cent total. She showed only a slight improvement with a high-protein, low-fat diet, and was again admitted the following year, when (2 years after the first operation) laparotomy was undertaken. The entire small bowel was found to be thickened and biopsy from the jejunum and stomach showed again a granulomatous lesion with pseudo-tuberculous follicles. No definitive surgery was possible. She remained in a state of extreme deficiency until 1955, four years after the first operation when, without any change in the supportive treatment, she started to improve. This improvement was very striking and the patient was able to do her housework and regained a nearly normal weight. In 1957, six years after the original operation, she became desperately ill with extreme diarrhœa, leading to dehydration and electrolyte and protein deficiency. She developed multiple perianal abscesses and fistulæ, and sigmoidoscopic appearances of severe ulcerative colitis. She has responded to ACTH treatment and is now (August, 1957) on the mend.

SUMMARY

1. One hundred and eight patients with Crohn's disease have been studied. Of these, 52 have been followed for more than 5 years and 30 for more than 10 years.

2. The recurrence rate in patients who had symptoms for more than 2 years before operation, and have been followed up for more than 5 years subsequently, was 65 per cent.

3. When the history before operation was less than one month, nearly all patients made a permanent recovery, only 12 per cent having suffered a recurrence.

4. When the history before operation is between 1 month and 2 years, 22 per cent of the patients followed more than 5 years developed a recurrence.

5. In two-thirds of the recurrences, symptoms of recurrence commenced within a year of operation.

6. Once the disease has recurred, it is unlikely to be brought permanently under control by medical or surgical means.

7. There is a relationship between Crohn's disease and ulcerative colitis. Several examples of this relationship have been encountered and reported.

8. When obstruction or fistula complicate the disease, operative treatment is indicated. In this series there is nothing to indicate the superiority of resection in one or two stages, short-circuiting, or short-circuiting with exclusion of the diseased segment.

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IDIOPATHIC MEDIASTINAL FIBROSIS

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ARGUMENT

Some surgeons do not agree that there is anything remarkable about idiopathic mediastinal fibrosis. It is, they say, the expected end-result of tuberculous mediastinal adenitis, syphilis, radiotherapy, or some comparable process. Perhaps they are correct.

The purpose of this paper is to submit theoretical reasons for contravening this opinion; to argue that it differs from fibrosis known to have been caused by chronic granulomatous conditions; to enumerate certain other diseases that are comparable in pathology and effect; and to do this because, if these things be true, the problem of treatment is peculiar.

IDIOPATHIC MEDIASTINAL FIBROSIS

To avoid confusion, idiopathic mediastinal fibrosis must be defined and some clinical description given. This name is used because the aetiology is unknown, because the site of the pathological changes is the mediastinum above the heart, and because an abnormal proliferation of fibrous tissue is the visible anomaly. The clinical hall-mark is the presence of venous hypertension in the catchment area of the superior vena cava. This hypertension is due to a fibrous mass that engulfs, invades, and destroys some or all of the great veins uniting to form the superior vena cava.

Incidence.—The disease is rare. It afflicts people of all ages and of both sexes; in general the onset occurs in middle or late life. Husfeldt and his colleagues (Anderson, Hansen, Husfeldt, Pedersen, and Thomsen, 1955) reported the case of a child aged 9 years whose symptoms had been present since the age of 2 years, and Blasingame (1938) treated a man who died from cerebral hæmorrhage at the age of 93 years; he had had superior caval obstruction for many years.

Some like to think that John Hunter described the first case in 1757; others prefer the description written by Hallet of Edinburgh in 1848. Certain it is that unexplained cases of superior caval obstruction caused by fibrous tissue have been described at intervals for more than a century.

Modern papers, and particularly those concerned with caval obstruction as a whole, generally emphasize that, when all has been said, a small group of cases remains in which the aetiology is unknown. For instance, Ochsner and Dixon (1936), reporting 120 cases, attribute 28 to "mediastinal fibrosis". They believed that, of this 28, 10 were due to tuberculosis, 11 were caused by syphilis, 1 was traumatic, 1 pyogenic, and 5 unknown. And Fischer (Fischer and Diss, 1904), whose cases were analysed by Ehrlich (1934) in Ballon and Graham's text-book, stated that 10 per cent of 220 were unexplained. Hinshaw in 1949 analysed 125 superior caval obstructions and 8 per cent were put down as due to "mediastinal fibrosis".

It is not suggested that any of these papers give a true picture of the incidence of idiopathic mediastinal fibrosis, but that they imply its existence.

The Clinical Picture.—As a rule the symptoms of this disease appear out of the blue in a patient who has previously been healthy. In taking the history it is natural to search for evidence of some previous malady such as an infection of the air passages or the lungs; but such a precursor is seldom evident, and if anything be discovered the connexion between it and the present complaint is tenuous and uncertain.

At the beginning superior caval obstruction is neither suggested nor obvious in many cases. The first symptoms are often intermittent and, being relatively mild, may pass unheeded. Sometimes the face swells for a few days, or a collar feels tight, and then the patient is well again for months. But there are records showing that severe and even fatal superior vena caval obstruction can overwhelm a patient in a few hours. One assumes that in episodes of this type spontaneous thrombosis of the cava must play a part.

In a typical case the first symptom is puffiness of the face and arms, noticed especially when the patient gets up in the morning. To this, in the second clinical phase, when the effects of superior vena caval obstruction are at their height, are added a dusky colour of the face, the neck and arms, with suffusion of the conjunctivæ and perhaps telangiectasis; dyspnœa, giddiness, tinnitus, headache, epistaxis, or hæmoptysis; a feeling of pressure in the head, and a dislike of crowded places. All these unpleasant features are aggravated by coughing, straining, stooping, or exercise. After about 6–9 months the patient enters upon the third phase of the illness in which, as the years pass, there is a progressive relief of many signs and symptoms. But the patient never again becomes totally free from disability. The disease is self-limiting and the harm it does cannot be completely overcome by nature. Apart from periods during which medical investigations are in train the patients usually remain ambulant and get back to their work.

There is no pain at any time in the illness unless axillary thrombosis is a complicating factor, nor is there fever. The blood-chemistry and the blood-count are normal. All serological tests are negative and the Mantoux reaction is equivocal. Bronchoscopy and œsophagoscopy are normal, and radiographs of the lungs and the mediastinum reveal neither tumour nor inflammatory disease. But the mediastinum may be broadened by distended parts of the azygos and hemiazygos venous systems (q.v.).

The face, the neck, the arms, and the upper part of the chest are generally, but not always, enlarged by œdema that does not pit. The lower parts of the body and the legs are normal. The other prominent feature is distension of the superficial tributaries of the superior vena cava and in these vessels there is no pulsation.

As the illness progresses many additional veins become visible at the base of the neck, on the front and sides of the chest, and along the costal margins. Sometimes they grow so large and tortuous that they dwarf all normal veins, and when this has happened they never regress and disappear, even though the caval obstruction may have been successfully relieved.

The pressure in the obstructed veins (which ranges from a few cm. to 20 or 30 cm. of water above the sternal angle) varies according to the phase of the disease. In the beginning the fibrous growth encroaching upon them partially obstructs the flow and the pressure is slightly raised; but when the lumen of the cava disappears the pressure becomes high and remains so until the collateral circulation has opened and provided alternative pathways. Venous collaterals produce no murmurs as do their arterial counterparts.

FIG. 239.—This venogram (*Case* 9) shows the great plethora of veins that open up as components of the deep collaterals. At this stage extensive communication with the hemiazygos and the azygos systems has not been established, but the intercostal veins, the internal mammary veins, and the lateral thoracic veins are already in use.

There are few signs apart from those typical of superior caval obstruction, but pleural effusions can occur and œdema of the glottis has been described. Husfeldt's patient, a child aged 9, had a large head due presumably to an increase in the pressure of the cerebrospinal fluid. Ferris (1939) has shown that the pressure in the cerebrospinal fluid is raised in caval obstruction. It is a curious fact that in superior caval obstruction the retinal veins do not appear to be distended.

Diagnosis.—Certain diagnosis, that excludes all the more common causes of superior caval obstruction, rests ultimately upon thoracotomy and biopsy of the fibrous tissue. The clinical feature that particularly suggests idiopathic mediastinal fibrosis is superior caval obstruction, causing venous hypertension in the upper part of the body, for which no clinical or radiological explanation can be found.

The essential investigation is to make venograms of the mediastinal veins.

Spontaneous thrombosis of the axillary vein is an anomaly that must be distinguished from caval obstruction caused by idiopathic fibrosis.

Venograms and the Collateral Circulation.—Venograms are an integral part of the diagnosis. They not only confirm the anatomical position of the obstruction, but they elucidate some abnormal shadows in the mediastinum that could be mistaken for tumours (q.v.). The patient is given a general anæsthetic and catheters are passed into a vein in each arm; 15 c.c. of 75 per cent diodone is injected simultaneously into each arm and serial radiographs, taken at second intervals, are secured.

Radiographs so made reveal a plethora of dilated tortuous venous channels, the majority of which are never seen unless the superior cava is obstructed (*Fig.* 239). The blood from the upper part of the body is chiefly carried through the azygos and the hemiazygos systems. These longitudinal vessels are components of the paravertebral system of veins; and they are particularly suited to take part in such a collateral by-pass because, through the superior intercostal veins, they communicate with the neck veins above; through the intercostal and internal mammary veins they drain the chest wall; and through the lumbar veins they open into the inferior cava below. The fact that they contain no valves is important because the direction of the flow can be reversed where necessary. By comparison with the azygos systems some of the superficial veins, and others like the internal mammary, distend until their valves become incompetent before they can carry a reversed flow; they are useless at first and only become important after being stretched beyond recovery. They are also subject to the effects of gravity. For these reasons a venous collateral circulation never becomes comparable in efficiency to its arterial counterpart.

The fact that the azygos and hemiazygos systems become two or three times larger than normal has an important diagnostic consequence. It has already been noted that plain radiographs of the chest show no tumour and no inflammatory mass in the mediastinum in patients having idiopathic mediastinal fibrosis. But the mediastinum is often widened in these cases, and sometimes there are obvious knuckle-like projections which create the illusion that the patient has a mediastinal tumour. These shadows are due to enormous collateral veins running along the side of the vertebral column and their true nature is beautifully revealed by venography. To mistake collateral veins for a tumour is a serious mistake, because the logical treatment for a tumour is radiotherapy and this makes mediastinal fibrosis worse.

The anatomical site of the obstruction is of clinical importance.

1. If it be above the superior cava, one innominate vein (usually the left) is spared. The clinical signs may not be diagnostic because the obstructed blood may be side-tracked through the cross-circulation in the neck (*Fig.* 240).

2. When the obstruction includes the superior cava, but is above the azygos vein, the collateral veins on the front of the chest do not become prominent, because the superior intercostal veins carry the blood into the azygos and so back to the heart (*Fig.* 241).

3. If the azygos vein itself is blocked as well as the superior cava, the collateral veins both inside and

outside the chest become dilated and they carry all the blood down to the inferior cava (*Figs.* 242, 243).

Surgical Pathology.—The descriptions in the literature of the abnormality that causes idiopathic mediastinal fibrosis are remarkably similar. They

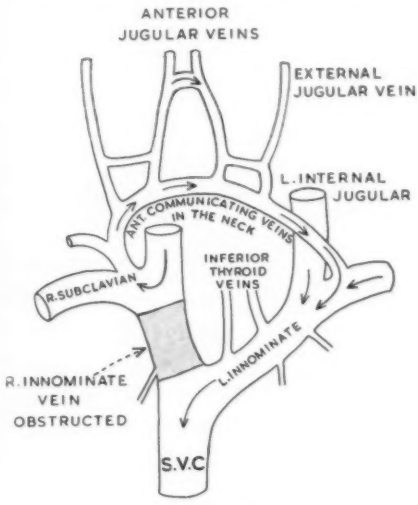

FIG. 240.

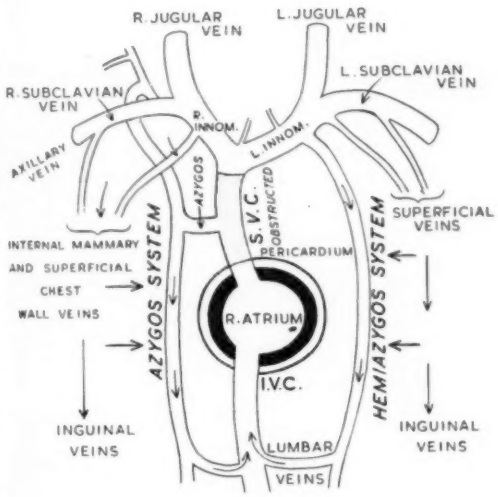

FIG. 242.

come from surgeons working in many countries and they describe their findings at thoracotomy. Autopsy reports are not so telling because they are seldom correlated with the history, and the consistency of the tissues alters after death. The following description is what the surgeon finds at operation.

In the front of the mediastinum, and usually situated towards the right side, there is a mass of woody, white, fibrous tissue. This varies in size from a lump like a plum to an indefinite plaque like a pancake. Sometimes this tissue is clearly circumscribed like a fibroma, but in the majority the limits are poorly defined. The most striking thing about it is that it is so hard and fixed that a malignant growth

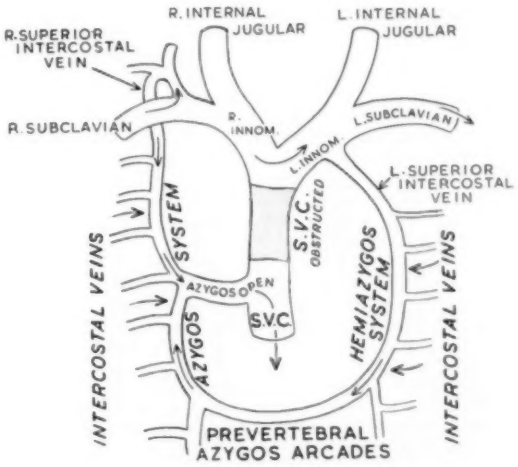

FIG. 241.

FIG. 243.—This photograph shows the early stages in the development of the superficial collateral venous circulation. The veins that become most obvious are those at the base of the neck, those in front of the sternum, and those in the mid-axillary line. The pre-sternal veins ultimately become very large and tortuous. (Infra-red photograph.)

is suspected, and the correct diagnosis can sometimes only be made by doing a biopsy and examining the tissue histologically.

The mediastinal pleura in the vicinity is thickened but not transgressed; that is, the lung is not invaded. The aorta and its branches, the trachea and the

œsophagus, the nerves and the thymus, become adherent to the mass and to each other, but the function of these structures is not impaired and no clinical signs referable to them develop. The mass of fibrous tissue may reach down to the pericardium but it never penetrates within it.

It is upon the superior cava and its radicals that the brunt of the destruction falls, though Erganian and Wade (1943) described one patient in whom the right pulmonary artery was also obstructed so that its lumen did not exceed 5 mm.

Histologically, the abnormal tissue consists of dense collagenous fibrous tissue that in parts is almost acellular. Throughout this are scattered areas of small round cell infiltrations and flecks of calcification or bone. The calcification never forms a plaque as it does in Pick's disease, and there is no caseation or liquefaction.

Veins and lymph-glands, if present, are engulfed. Histological sections of great veins that have been invaded show their walls destroyed and replaced by fibrous tissue that is dense and avascular.

Sometimes one or two lymph-glands are included and these may show any of the changes that are commonplace in mediastinal nodes; but they are often normal in anatomy, and do not convey the impression that they have caused the disease, nor is it usual to find enlarged or abnormal lymph-glands in the hilum of the lung.

It is, of course, true that aggregates of pathological glands such as occur in tuberculosis, sarcoidosis, lymphomas, malignant disease, etc., can cause obstruction of the superior cava; but when this happens other structures, such as the trachea or nerves, nearly always suffer as well. In idiopathic mediastinal fibrosis it is peculiar that only the great veins become involved.

Cultures made from tissues removed at operation are always sterile. Some writers have suggested that virus or fungus infections are the cause, but there is no proof of these opinions. Syphilis, so often used as a scapegoat, is not responsible for this disease.

The following suggestions have been made as to the aetiology. None is acceptable in the present writer's opinion.

1. Tuberculous lymph-glands can become matted together and adherent to vessels; they can also caseate and, in healing, be replaced by scars. But histologically some remnants of tuberculosis remain in most cases and, a point which is more important, tuberculous adenitis seldom produces vena caval obstruction. Those who favour tuberculosis as the cause say that the fact that the histology is not typical and that the bacilli cannot be found is not decisive, because similar tissue is found in Pick's disease. That is generally caused by tuberculosis, and by the time the surgeon comes to operate all traces of tuberculosis have often disappeared. Moreover, if tuberculosis be the cause, it is strange that idiopathic mediastinal fibrosis is confined to the vicinity of the superior vena cava, whereas tuberculous glands occur more commonly elsewhere in the mediastinum.

2. Actinomycosis and other chronic granulomata could theoretically produce the changes, but few believe that they do.

3. Clagett (Kunkel, Clagett, and McDonald, 1954), reviewing 32 cases of mediastinal granulomata (whose nature had been proved by thoracotomy and histologically), pointed out that practically all these tumours occurred in the same region as idiopathic mediastinal fibrosis; that about 50 per cent were cystic and contained a white cheese-like material, and that several appeared to be on the point of bursting at the time they were removed. In these cases no specific organisms were demonstrated, no cause found, and superior vena caval obstruction was unusual. But, Clagett asked, what would happen if such a cyst were to rupture into the mediastinum? It could conceivably produce a spreading, aseptic, fibrous inflammation. If this were to happen one might expect some clinical history of prolonged mediastinal disease and the episode of rupture would surely leave its clinical mark.

4. Some have considered the lesion to be inflammatory, and have reconciled the lack of organisms by stating that their absence was due to chemotherapy. But idiopathic mediastinal fibrosis existed before chemotherapy was available.

5. Organization of a hæmorrhagic exudate has been blamed by those who have found blood-pigments in the fibrous tissue, but it is difficult to understand the mechanisms which could produce such results in the mediastinum.

The Prognosis.—The risk to life, both immediate and ultimate, is small, except in those rare cases where total superior caval thrombosis occurs within a few days. (Ochsner and Dixon (1936) have stated that the mortality of superior vena caval thrombosis was 73 per cent in the acute phase.) The inconvenience, however, is considerable and sustained. As time passes the development of the venous collateral circulation mollifies some of the distress, but the clinical state never returns to normal unless the mechanical obstruction can be overcome.

Watching these patients over the years one observes that idiopathic mediastinal fibrosis is a self-limiting disease; that is, whatever caused the fibrosis ceases to operate, leaving a space-occupying lesion which not only causes no additional trouble but tends to shrink. Thus the patient's condition improves in regard to the degree of venous distension, and the cyanosis and œdema become less obvious. Nobody has suggested that the superior vena cava or its radicals recanalize in this disease.

Treatment.—Medical treatment is of no avail at any stage. Antituberculous and antisyphilitic drugs do nothing; cortisone and heparin are disappointing; radiotherapy is harmful.

Until recently surgical endeavours were uniformly unsatisfactory. They achieved nothing and carried an operative mortality (Tubbs, 1946), but a few patients have been cured and this encourages further endeavour. The truth remains, however, that operation should only exceptionally be recommended.

DISCUSSION

The practical reason for considering idiopathic mediastinal fibrosis as an entity—at least until the cause can be identified—is that once obstruction has developed the surgeon can assume that the affected veins are destroyed beyond release or recanalization. This is in contrast to obstructions produced by lesions such as mediastinal goitre, where the cava is not invaded but stretched over the mass, or obstructions

due to lymphomata and other tumours that are radio-sensitive, in which the symptoms can be temporarily alleviated. Obstructions due to tuberculosis and to syphilis (if such exist) carry a different prognosis and require special treatment.

Some theoretical reasons that favour the idea that idiopathic mediastinal fibrosis is different from all of these things may be stressed at this point.

1. The disease strikes out of the blue in a fit person. No infection or new growth is culpable, and no cause can be found.

2. Unlike axillary vein thrombosis the onset is gradual (extending over a period of weeks or months), there is no pain, no fever, and the damage to the veins is permanent.

3. The tissue causing the obstruction is very hard, and is always found in the same part of the mediastinum.

4. No organisms can be incriminated.

5. The disease terminates as mysteriously as it starts, but many of the symptoms remain.

COMPARISON BETWEEN IDIOPATHIC MEDIASTINAL FIBROSIS AND OTHER DISEASES OF FIBROUS TISSUE

If one argues that idiopathic mediastinal fibrosis is a specific entity and not merely a scar of healed tuberculosis, a variety of speculations are opened for scrutiny.

In broad terms one may regard diseases that affect fibrous tissue as falling into three categories.

1. The first are the collagen diseases; these are not related to the present subject. They include periarteritis nodosa, disseminated lupus erythematosus, rheumatic fever, rheumatoid arthritis, etc., and they have in common certain features that separate them from idiopathic fibrosis, namely: fever, a raised E.S.R., a tendency to joint manifestations, specific changes in the gamma-globulins of the serum, a probable response to cortisone therapy or ACTH, etc.

2. The second group includes Dupuytren's contracture of the palmar fascia, Peronie's disease (induratio penis plastica), keloids in the skin, fibrous dysplasia of bone, etc. There is no known aetiology, no evidence of inflammation, no systemic effects, a constant histological picture, and a predictable clinical course. In these respects these diseases resemble idiopathic mediastinal fibrosis; but there is a different quality to the fibrous tissue. In these conditions it is not iron-hard, it is not like carcinoma to feel, and it does not engulf adjacent structures.

3. The third category resembles idiopathic mediastinal fibrosis pathologically and the conditions that follow could perhaps be related. Because they occur as rarities in the practice of different specialists they have not to my knowledge been compared as yet.

a. The pathology of **periureteric fibrosis** (idiopathic retroperitoneal fibrosis) is, according to an annotation in the *Lancet* (1957) "baffling in its simplicity. There is progressive fibrosis, spreading laterally from the great mid-line vessels gradually engulfing, distorting and finally strangling both ureters." In 1958 Hackett published a good review of the subject. He stressed the retroperitoneal site of the lesion and stated that Ormond (1948) was the first to recognize it as an entity. In addition to destruction of the ureters, Chisholm, Hutch, and Bolomey (1954) reported œdema of the legs and scrotum due to inferior vena caval involvement and Paull, Causey, and Hodges (1955) had a patient in whom the mass was palpable. No primary cause has ever been found. The general signs and symptoms do not suggest bacterial invasion; histologically the tissue consists of dense collagenous fibrous tissue; the lymph-nodes, that may be included, are normal; fever is absent; the laboratory tests are all negative; and ill-health is delayed until the onset, sudden or gradual, of renal failure. The process, whatever it be, is self-limiting, and if it ceases before the ureters have become irretrievably obstructed, the patient may survive (Miller, Lipin, Meisel, and Long, 1952; Raper, 1955; Ormond, 1948; Ross and Tinckler, 1958).

Discussing the anatomy and the aetiology of 'idiopathic retroperitoneal fibrosis' Hackett expressed the following opinions:—

i. "The boundaries within which this disorder occurs are very definite. In only one instance (Raper, 1956, *Case* 7) has it been seen extending above the hila of the kidneys. . . . Laterally the lesion does not pass a line running 1 cm. on the lateral side of the ureters. Below it stops at the pelvic brim. In no case has it extended anteriorly into the mesentery or around the cœliac or mesenteric arteries. These limited boundaries correspond to those of the renal fascial compartments."

It will be remembered that idiopathic mediastinal fibrosis appears to be confined to the vicinity of the superior cava and that it does not invade the pleura, the lung, or the pericardium. The present author knows of no fascial compartment that could be said to contain and define mediastinal fibrosis.

ii. In a review of possible causes of retroperitoneal fibrosis diseases of the lymphatic vessels or glands are not considered by Hackett as a cause. Lymph-glands may be included in the fibrosis.

iii. Hackett suggests that the most likely cause is trauma leading to an exudate of blood and so to hæmatoma. The renal fascial space is an area from which such an exudate might not easily be removed. It might organize and form collagenous fibrous tissue; it seems doubtful if trauma could account for mediastinal fibrosis.

In 1946 Tubbs recorded an important case, in which a patient upon whom he had operated died and was found to have not only mediastinal fibrosis, but periureteric fibrosis as well. This case history suggests to me that the same factors operate in mediastinal and in periureteric fibrosis.

A man, aged 25 years, enjoyed good health until 1941; he then complained of tiredness and of having coughed up some blood-stained sputum. He was admitted to a sanatorium, but nothing abnormal was found and he was discharged. A year later his face and neck became swollen and his eyes were watery. Once again the symptoms subsided and he remained well for a year. After this the trouble recurred and on admission 6 months later he had the characteristic features of superior vena caval obstruction. Apart from this, physical examination was negative, but radiographs showed some widening of the mediastinum and a few calcified lymphatic glands. Thoracotomy was done and revealed the typical features of idiopathic mediastinal fibrosis and the lesion was judged to be inoperable. The patient died on the ninth post-operative day. At autopsy the cellular tissue of the mediastinum

was seen to be replaced by dense fibrous tissue in which numerous enlarged lymphatic glands were embedded. Calcified glands were present in the hilum, but there was no calcification or caseation in the glands that were embedded in the mass. The superior vena cava and the azygos vein were totally obstructed. When the abdomen was opened the same massive fibrosis was found in the para-aortic region, and this had caused stenosis of the inferior vena cava at the level of the renal veins. Distal to this point a recent thrombus occluded the inferior vena cava and extended into both iliacs. The state of the ureters is not described, but the picture of the autopsy specimen indicates that they must have been surrounded.

b. In 1850 Flarer reported that the Austrian Field-Marshal Radetsky was suffering from malignant disease of the orbit. Contrary to expectation he did not die and in the light of modern knowledge it is probable that he was suffering from **pseudo-tumour of the orbit.**

Duke-Elder, in his text-book on ophthalmology (1952), stated that it is not doubted that an ill-defined group of cases exists that exhibit this type of non-specific inflammatory response, and that many exenterations of the orbit have been performed on a mistaken diagnosis of cancer.

Harvey Jackson (1958) makes the following observations about this condition. He regards these 'granulomatous diseases' (by which tuberculosis is not indicated) as the commonest cause of orbital proptosis and has had experience of 37 cases. The pathological changes are said to start in the orbital muscles (although how this is known is difficult to understand) and by the time operation is done to relieve the exophthalmos a mass of fibrous tissue, resembling carcinoma in its hardness, occupies the orbit. The muscles are invaded and lose their striation, and the fibrous tissue burrows between, and encircles, everything in the orbit. Sometimes it forms a discreet palpable mass and sometimes it is diffuse. Nerves are never involved or paralysed and the optic disk remains normal, but veins are obliterated.

This disease seems to progress to a certain point and then, like the others already described, to become quiescent and regress. No specific organisms have been described and there is nothing to suggest inflammation as the cause, although the proximity of the air-sinuses directs attention to this possibility. The fibrous tissue removed at operation varies in its consistency; sometimes it is collagenous and practically acellular, but at others it contains a small round-cell infiltration. There is nothing to incriminate syphilis or tuberculosis.

As there are no lymphatic glands in the orbit these cannot be the starting point of the fibrosis.

No cases have been recorded of idiopathic fibrosis elsewhere in the body as a complication, but the other orbit is often involved.

c. In 1896 Reidel described a unique process affecting the thyroid gland that led to an extraordinary iron-hard tumour, firmly bound to the surrounding structures. The large blood-vessels of the neck and the trachea could not be separated from the mass, which suggested that it was an inoperable growth, but microscopic examination demonstrated infiltration and compression of the thyroid tissue by scar. The aetiology of Reidel's disease has remained in doubt, and many (Vaux, 1938) consider it to be a terminal stage of Hashimoto's struma. For our purpose De Courcy's (1942) theory is interesting, namely, that Reidel's disease "begins as a perithyroiditis and results in constriction of the thyroid vessels and associated blood channels", that is, the changes in the thyroid are secondary to cervical fibrosis. In this disease the cervical lymphatic glands become involved, but nobody suggests either that they are the primary cause or that tuberculosis is to blame.

SURGICAL TREATMENT

Surgeons have always felt that technical problems are capable of solution; it should be practical to relieve the symptoms of idiopathic mediastinal fibrosis. The facts are simple; the fibrous overgrowth itself cannot be dissected out without removing the important veins that pass through it; the blood, obstructed in the territory drained by the superior vena cava, must be given free access to the right atrium; and the channels through which it is routed must function as efficient veins. An operation would be worth while if the chances of symptomatic relief were good, because the disease is self limiting, although some of the symptoms are permanent.

It is surprising that relatively little research into the question of how to circumvent caval obstruction appears to have been done. The problem is not sufficiently urgent to occupy more than the transient attention of those most likely to solve it. Many have toyed with the idea: few have persisted. It is to Gerbode and his associates (Gerbode, 1954; Gerbode, Yee, and Rundle, 1949) that most of the credit goes.

Attempts to free the obstructed veins by paring away successive layers of fibrous tissue until the wall of the cava is exposed have been recorded. Such operations cannot succeed unless venograms show that a remnant of a channel exists in the obstructed segment of the vein. Sometimes the obstruction is produced by a limited mass of fibrous tissue like a plum; by incising the 'tumour' down to the vein the latter may be sufficiently freed to improve the circulation. O'Neill (1954) has shown that upon occasion it is feasible to core out an obstruction; but the risk of recurrence must be high and, considering the usual pathology, the chances of finding suitable cases small.

An attractive solution would be to by-pass the blocked vein with a graft. Technically this is easy to accomplish, but the operation fails so often that surgeons despair of using it. Thrombosis is almost certain in the graft. Nevertheless, successes have been claimed, and especially during the last five years.

In 1951 Klassen, Andrews, and Curtis described a successful vein-graft, and in 1954 Scannell and Shaw added two others; these were probably the first good results. The discussion that followed Scannell and Shaw's paper was useful because many of those most qualified to speak took part. The following points were mentioned in this discussion.

In 1948 Gerbode and his associates successfully anastomosed the vena cava to the auricular appendage in animals. The pathology of idiopathic mediastinal fibrosis makes it unlikely that this manœuvre would be applicable in man (Gerbode, Yee, and Rundle, 1949).

Kay (1954) reported that the superior vena cava of one dog could be successfully grafted into another and that venograms done 6 months later showed that 30 per cent of the grafts were patent. But when the dogs were ultimately killed all the grafts were obstructed. This showed that good results probably would not last.

Deterling (1954) reported the same kind of results as Kay, but he had used aortic homografts; and Gerbode (1954) stated: "In every instance in which we used an aortic homograft, thrombosis or gradual fibrosis occurred."

These grafts fail because of thrombosis, particularly at the two anastomoses. The reason for this is that although the venous pressure is raised at the time of the operation, it drops if the graft succeeds. Various attempts to circumvent this deficiency have been made; these include using the atrial wall instead of the auricular appendage for the lower anastomosis, using the stump of the superior vena cava inside the pericardium for the lower anastomosis (a generous length of vein is available because the fibrosis does not transgress the pericardium), using very large grafts, and trying to place stents inside the lumen at the points of suture.

Husfeldt (Anderson and others, 1955) has shown that in a favourable case the azygos vein can be used as a by-pass, not by turning it up but by turning it down. The fact that the present writer has had a similar experience shows that these cases are not curiosities.

PERSONAL EXPERIENCES OF IDIOPATHIC MEDIASTINAL FIBROSIS

The following patients, who were not explored surgically, were assumed to be suffering from idiopathic mediastinal fibrosis, because the clinical signs and symptoms suggested this diagnosis.

CASE REPORTS

Case 1.—This patient, a hospital barber aged 44 years, had his first symptoms in 1944. He noticed giddiness when he got up in the mornings. After this his face gradually became swollen and dusky in colour, and his arms felt heavy. On admission to hospital he had the typical signs of superior caval obstruction, but no cause was found to account for this. All laboratory tests were negative and the radiographs of the lungs and the mediastinum were not informative.

As it was believed that the condition must be due to a hidden malignant growth in the mediastinum the patient was given a short course of radiotherapy, which was abandoned as it made the symptoms and signs worse.

During the past 15 years he has been working as a barber in the hospital and has been under continuous observation. He has always been able to do his work, except during a number of short illnesses in which he has suffered from bronchitis and from hæmoptysis on one occasion. He complains of fullness in the head and dizziness whenever he bends down, and dislikes travelling in the rush-hour because the crowds make him feel faint. Apart from these troubles, he has no complaints and manages reasonably well.

Over the years the cyanosis has not changed much; the neck veins are always distended and large tortuous veins have appeared upon the front of the chest and in the mid-axillary lines. There is no œdema of the arms, and the peripheral pulses are regular and equal everywhere. The heart-sounds and blood-pressure are normal. The chest is barrel-shaped and moves poorly, but apart from episodes of bronchitis, there is no other disease. The abdomen is normal. The clinical state has, in effect, not changed since the symptoms and signs became established.

Venograms made in 1955 show that both innominate veins are blocked so that no blood enters the superior cava. The azygos and hemiazygos systems are greatly distended and tortuous, the cross-communicating channels are evident. On the right side the collateral circulation from the innominate vein passes by way of the superior intercostal into the azygos, in which the flow is reversed towards the abdomen. The intercostal veins are large, but the ribs are not notched. The internal mammary and phrenic veins are conspicuous, as well as a host of unnamed superficial channels.

The circulation times are arm to lung, 30 seconds (normal 3-9 seconds) and arm to tongue, 35 seconds (normal 8-16 seconds).

Comment.—This history illustrates the usual course of this disease. The disabilities are at their worst in the first few months and from then onwards not only do the symptoms improve, but the patient learns to live with his disease. The development of collateral channels alleviates some of the harmful effects of superior caval obstruction, but achieves this at the expense of superficial anomalies in the shape of obvious tortuous subcutaneous veins.

Case 2.—A Naval stoker, aged 24 years, reported sick in July, 1951, because his neck became swollen one day as he was working in the boiler room. He was admitted to hospital in 1951 and had the signs of superior caval obstruction at that time. He stated that the onset of symptoms was intermittent at first and not bad enough to cause anxiety.

The face and neck were cyanosed and the arms moderately swollen. The heart and systemic vessels were normal, but the cervical and arm veins were much distended. The conjunctivæ were a little œdematous in appearance. A particularly large vein was present in the suprasternal notch and there was a suggestion of a palpable firm mass behind the sternum, but there was some doubt about this observation.

Radiographs of the chest revealed nothing of interest in the lung fields or the mediastinum, but there was a palpable gland in the right axilla. This was removed and it showed lymphoid hyperplasia. There was no evidence of tuberculosis, lymphoma, or new growth. In spite of these negative findings a course of radiotherapy was given without benefit, and after this the patient was transferred to my care.

Shortly after admission the swelling of the head and neck became worse; the right axillary vein became painful, hard, and palpable; the patient complained of an intense, throbbing, headache; and the superficial veins in his arms were distended. He was given a course of anticoagulants and the acute symptoms gradually subsided, leaving cyanosis and the signs of caval obstruction. Another axillary gland was removed, but it was not helpful histologically.

All laboratory tests were negative, and the lung fields were clear, but there was widening of the mediastinum which was wrongly considered to be due to a tumour in that area.

Venograms were made a year later at a time when the venous thromboses appeared to be quiescent; these showed the right axillary vein to be patent as far as the outer border of the first rib. The innominate veins and the superior cava could not be visualized, but a massive collateral circulation was present, and this accounted for the broadening that had been observed radiologically in the mediastinum.

No further treatment has been given and the clinical state has remained unchanged during the past 7 years.

Comment.—This patient was diagnosed at first as suffering from malignant disease of the mediastinum and the prognosis was discussed with him. When he did not deteriorate as anticipated, the diagnosis was changed to superior caval thrombosis and appropriate treatments were prescribed. Neither radiotherapy nor anticoagulants did good. The clinical course of this man's illness is suggestive of idiopathic mediastinal fibrosis, and the history illustrates that it is unwise to give a firm diagnosis as to the cause of superior caval obstruction when no cause can be found.

Case 3.—A man, aged 40 years, was admitted in 1952 with a history of repeated small hæmoptyses. He had suffered from hæmoptyses since 1933 when he stated that he had had an attack of pleurisy. He was discharged from hospital feeling well, but 4 days later, after sleeping in the garden in the sun, he woke to find his face swollen. This affected the right side first, but soon involved the left and also the neck. The arms became 'heavy'. Just after this he had his first small hæmoptysis and complained of dyspnœa. He was admitted to a sanatorium because it was thought that tuberculosis was the probable cause, but nothing to substantiate this was found, and he was then sent to a general hospital, where malignant disease of the mediastinum was suspected and radiotherapy prescribed.

After this his symptoms regressed a little and he was discharged. The dyspnœa had improved, but the cyanosis of the head and neck persisted. About 4 months later he coughed up 1 pint of bright red blood, and ever since then (i.e., for 19 years) this symptom persisted, although in recent times the bleedings have been less severe and occur at longer intervals. Between attacks he feels well and has continued to work as a telephonist.

He was admitted to hospital in 1952 under my care because of a recent more serious hæmorrhage, and his signs and symptoms were those of superior caval obstruction, for which no cause could be found. At bronchoscopy a little old blood was seen in the orifice of the right upper lobe bronchus, but there was no distortion of the bronchial tree, and no tumour was present. Bronchograms and radiographs of the lungs and the mediastinum were normal. The Mantoux reaction was negative to 1 in 100, and no significant organisms were cultured or found in the sputum. All laboratory tests were negative; there was no fever.

The patient left hospital and returned a year later for assessment. In the interval he had been well and there had been no further hæmoptyses. He was working full-time, but the signs of superior caval obstruction had persisted in a reduced form.

Venograms showed complete obstruction of the innominate veins; the superior cava was not filled, but a great collateral circulation was apparent. No tumour was seen in the mediastinum.

He was last seen in December, 1956, that is, 33 years after the onset of his symptoms, and he stated that the hæmoptyses had ceased, he felt well, and was doing full-time work. The puffy appearance of the face and neck had not changed. He said he could carry on without treatment.

Comment.—Hæmoptysis is a recognized complication of superior caval obstruction and may be due to an increase of pressure in the bronchial veins. This man, who has now settled down completely to living with his symptoms, has had idiopathic mediastinal fibrosis for at least 36 years; he needs no treatment, though his physical signs are still obvious.

The following cases underwent operation; all but one are failures: one is a complete clinical success:—

Case 4.—A mechanic, aged 32 years, was admitted for investigation of hæmoptysis. He had always been healthy and had never been to a doctor before. The present trouble started while he was digging in the garden. The bleeding was not severe, but continued as blood-staining of the saliva for several days. He had one episode in which, on coughing, he brought up about an egg-cupful of bright red blood.

On admission he had the typical signs of superior caval obstruction. These were mild and were not at first obvious to the patient. All examinations were negative and the radiographs were normal. After 3 weeks the distended veins subsided and he was discharged from the hospital.

Six months later, having had no troubles in the interval, he was admitted again with a swollen neck and on this occasion the signs of caval obstruction were obvious. The face, neck, and arms were cyanosed and swollen and there were prominent veins on the front of the chest. There were no other physical signs. All laboratory tests were normal, as were radiographs of the lungs and mediastinum; venograms showed caval obstruction at the level of the azygos vein.

On July 10, 1954, a right thoracotomy was done. The lung and the pleural cavity were normal, but there was a hard white mass of tissue compressing and obliterating the vena cava at and below the entry of the azygos vein. The pericardium was opened and everything inside this was normal. No lymph-glands were seen, and a frozen section revealed the tissue to be hyaline fibrous tissue which was almost acellular. The azygos vein was large and dilated and with a little mobilization it could be approximated to the top of the intrapericardial part of the superior cava which was cut across. An end-to-end anastomosis between the azygos vein and the butt-end of the superior cava was performed.

Convalescence was uneventful; there was some clinical relief of the caval obstruction, although dilatation of the cervical veins remained. The patient was followed up for 4 years and during this time he remained at work. On two occasions there have been mild hæmoptyses. The swellings of his arms have disappeared, but he still has some signs of superior caval obstruction. On the whole he is improving and his disease is stationary.

Comment.—Considering the anatomical position of this obstruction, one could not hope to get complete relief of symptoms by freeing the azygos, because the superior cava remains obstructed. Unfortunately, it has not been possible to get late venograms, so no assumptions as to the patency of the anastomosis are justified.

Case 5.—A man, aged 53 years, was admitted in October, 1954, with a history recounting that in June, 1953, he had had a sudden attack of unsteadiness during which he fell to the ground. Ten days later, while driving a car, he 'blacked-out' completely. A month after these episodes he noticed an enlargement of the left side of the face and neck. The puffiness steadily increased in extent and was accompanied by dyspnœa. The swelling of the face and neck became general and was at its worst when the patient lay down. He had had several more 'black-outs', particularly after coughing.

He was admitted in October, 1954, and had all the typical features of superior caval obstruction. Apart from these there were no abnormal signs; the radiographs and tomograms were normal, as were all laboratory tests. The Mantoux reaction was negative. Venograms showed that there was an obstruction at the junction of the left and right innominate veins. Bronchoscopy and œsophagoscopy revealed no cause for the obstruction.

On January 5, 1955, the anterior mediastinum was exposed by splitting the sternum. The right innominate vein was thrombosed as far up as the thoracic outlet; the left innominate vein was large and adherent to a block of tough fibrous tissue in the mediastinum, and on dissecting the parts it became apparent that the region of the origin of the superior cava was occupied by a hard white fixed mass, into which the great veins disappeared and from which extensions spread out in various directions. The obstructing mass involved the superior cava to a point below the azygos vein. A biopsy of this tissue showed it to be nothing but scar, but it also included a remnant of normal thymus. It was decided to by-pass the obstruction by inserting a graft of orlon between the distended left innominate vein and the right auricular appendage. At the conclusion of the operation the graft functioned perfectly, and the anæsthetist said that the colour of the face and neck had improved. A fine catheter was left in the left cephalic vein and the tip of this lay at the upper end of the graft. Through this a solution of heparin was dripped into the vein for 7 days.

Three weeks later the wound became infected and started discharging pus. Two days prior to this the symptoms of superior caval obstruction had returned and it was obvious that the operation had failed. During the following months the wound was explored and the graft removed. The orlon was lying free in a small abscess cavity; it contained no thrombus and the original sutures were still in both ends of the tube. The wound healed by first intention.

The patient has been seen regularly during the past 3 years. The signs and symptoms of superior caval obstruction remain, and cause moderate embarrassment while he is at work. If anything, he is getting slowly better, and now has obvious collateral veins running down the front of the chest. His dyspnœa is less than it used to be.

Comment.—This man seemed at first to be relieved of his obstruction until the wound became infected, but considering the experiences of other surgeons one must doubt the wisdom of using an orlon graft. It was used on this occasion in the hope that, by inserting a by-pass of large diameter (and this one was about 1 in. across) thrombosis might be avoided.

Case 6.—A housewife, aged 22 years, who had had no previous illnesses, complained that for 4 months she had felt giddy whenever she bent down. For 3 weeks she had noticed prominent veins in the neck, but otherwise there were no symptoms.

She was admitted with the typical signs of superior caval obstruction, and no other physical signs were found.

Radiographs revealed nothing abnormal, but tomograms suggested that there was a mass in the right side of the mediastinum. The trachea and the œsophagus were not affected. Venograms showed extreme narrowing of the superior cava, which was curved as though it was passing round a mass that was not only distorting the vein, but displacing it sideways. A small channel, like a piece of string, remained. All serological and laboratory tests were negative.

On November 29, 1949, mediastinotomy was performed. The mediastinum was exposed by splitting the sternum. The obstruction was produced by a circumscribed white hard lump, situated at the origin of the superior vena cava and reaching down to the pericardium. The azygos vein was obstructed as it entered the 'tumour'. Believing the mass to be a carcinoma a rapid smear was made, but this revealed nothing but fibrous tissue and a few small round cells. There were no enlarged lymph-glands and the thymus was normal. In the hope of relieving the obstruction, as much as possible of the fibrous tissue was shaved off from the front of the vena cava. In this way the innominate vein on the left side was freed and the lumen of the superior cava was improved, although it was impossible to dissect this vessel free.

Convalescence was satisfactory and the physical signs of caval obstruction were relieved. A venogram made before the patient left the hospital showed that the lumen of the superior cava was about twice as large as before operation, although it was still deformed; both innominate veins were patent. She was seen regularly until 1955 (i.e., 6 years). At that time she seemed to be without symptoms and had no physical signs of caval obstruction.

Comment.—Although this patient has been relieved of the symptoms of caval obstruction, normal venous flow has not been re-established. The result encourages one to persist with experimental work, because this disease is self-limiting and could be cured by a graft that did not clot.

Case 7.—A toolmaker, aged 22 years in 1952, was admitted with a history that his face and head felt as though he had "been standing on them". He only got this peculiar feeling when taking exercise; otherwise he was well. His arms were not swollen. His symptoms got better at night, but his head and face felt 'blown up' when he stooped to put on his shoes. He had some dyspnœa of recent origin, but otherwise there were no complaints.

On admission he was found to be healthy in appearance, but he had distended veins in the neck; there was no pulsation in the veins. The face was rather dusky, the arms were not œdematous, and there were no physical signs elsewhere. A little sputum was collected and this was negative for tubercle bacilli.

Radiographs showed infiltration of the right upper lung field, possibly due to tuberculosis, and tomograms outlined a small 'tumour' in the right mediastinum near to the azygos vein. All laboratory tests were negative and there was no evidence of active inflammatory disease. Cardiac catheterization showed a resting pressure in the right innominate vein of 17 mm. Hg and this rose to 34 mm. Hg on exercise. With difficulty the catheter was made to enter the right atrium and the pressures in the right heart were normal. The venograms showed dilatation of the innominate veins and of the superior cava as far as the azygos; beyond this point the lumen was reduced to the size of a fine piece of string. There was only a moderate development of collaterals.

On May 23, 1955, the mediastinum was exposed by cutting the sternum vertically. The obstruction was similar to that described in *Case* 4: it consisted of a thick flattened plaque of dense fibrous tissue situated at the point where the azygos vein joined the superior cava. It was not possible to remove the obstruction, and so an orlon graft was put in from the left innominate vein to the right auricular appendage. There was no technical difficulty and a good flow distended the graft. On examining the right upper lobe of the lung healed pulmonary tuberculosis was found, but there was no tuberculosis in the hilum and no glands were seen. Histological sections of the tissue causing the obstruction were examined and none showed tuberculosis.

On returning to the ward the patient was extremely cyanosed in the face and arms, and this discoloration remained for several days, after which it resolved slowly.

A venogram done 6 weeks later revealed complete caval obstruction. The graft was patent as far as the anastomosis with the auricular appendage, but this was closed.

A year later the patient's symptoms were unrelieved and his general condition unchanged.

Comment.—This patient, whose obstructing lesion may have been due to old tuberculosis, is

included because the orlon graft nearly succeeded. It remained patent (for 6 weeks at least) except at the lower anastomosis. Some of my colleagues felt that it would have been preferable to join it to the wall of the atrium.

Case 8.—A housewife, aged 45 years, was admitted in 1952. Her complaint was of dyspnœa and distended veins upon the front of the chest of 18 months' duration. She had first come to hospital 14 years previously when she was pregnant and suffering from a goitre. After the baby

FIG. 244.—This is the anteroposterior view of the chest and mediastinum of a woman (*Case* 8) who was diagnosed as suffering from a malignant mediastinal tumour. In fact she had caval obstruction due to idiopathic mediastinal fibrosis and the broadening of the mediastinal shadow is due to great and tortuous dilated, azygos veins (*see Fig.* 245).

was born a nodular goitre was removed by Mr. C. Joll and she remained well until 1950. The following year another baby was born, and after this she developed a hernia that was repaired.

The symptoms of caval obstruction started gradually and, at first, only the right side of her neck was swollen. She was thought to have a recurrent thyroid.

By the time of admission to my ward she had a large, swollen, heavy right arm and the signs of superior caval obstruction of moderate degree. An extensive collateral circulation existed. No thyroid tumour or enlargement was felt. There was no dyspnœa, no mass palpable, and, in fact, no demonstrable cause for the obstruction. All laboratory tests were negative. Radiographs of the chest were normal, but there was a definite mass seen to be widening the mediastinum (*Fig.* 244). This was wrongly diagnosed as a tumour.

Venograms showed that the superior cava did not fill but that the innominate veins were patent as far as their point of union. The shadow that had been mistaken for a tumour in the mediastinum was caused by greatly distended hemiazygos veins (*Fig.* 245). Fortunately, the error was appreciated before radiotherapy could be given or the prognosis discussed.

The mediastinum was explored by a vertical sternal split in 1953. A large hard plaque of white tissue surrounded and obstructed the superior cava. This tissue was thought to be a malignant growth and, since the prognosis was judged to be hopeless, the mediastinum was closed without attempting a by-pass.

Convalescence was uneventful and the biopsy material showed no evidence of growth, merely dense collagenous fibrous tissue, which was almost acellular.

This patient is alive and well 7 years later. Her symptoms are unchanged and her principal trouble is the heavy and big right arm.

Comment.—Some of my colleagues considered that the mediastinal fibrosis might have been due to the thyroidectomy. The notes of this operation stated that in removing a small mediastinal extension of the thyroid a lot of colloid was spilt into the wound. No colloid was found in our histological sections.

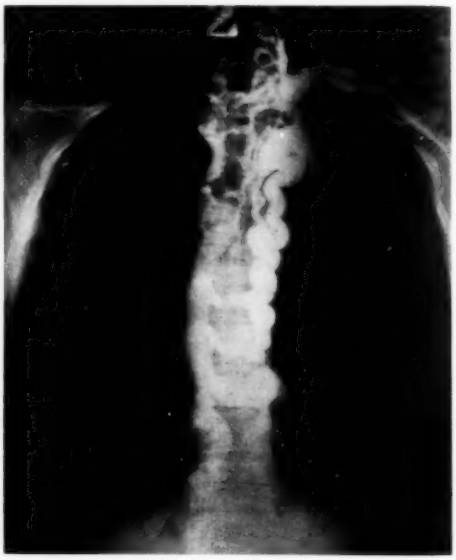

FIG. 245.—Venogram showing that the mediastinal widening shown in *Fig.* 244 is due to the deep collateral elements of the azygos and paravertebral systems of veins.

The fact that even after some experience of idiopathic mediastinal fibrosis one may still mistake the lesion for a malignant growth is unimportant; the shadow that enlarged the mediastinum in radiographs and that was caused by collateral veins presented another pitfall.

Case 9.—A dustman, aged 34 years, was admitted in October, 1957, complaining of headaches of 5 years' duration. He had always been healthy and had served with distinction as a commando during the second world war.

No reason could be found for the onset of the headaches; his vision and hearing were normal. The headaches were of the frontal type and were getting more serious, so that he found it difficult to do his work. When first seen in the out-patient department there were no physical signs and he was discharged undiagnosed, but the trouble continued and he reported again some months later. By July, 1957, he had developed 'contraction of the throat' and his face, neck, arms, and hands were puffy. His collars would no longer fit. He then had the signs of superior caval obstruction. Two courses of radiotherapy were given, although no cause had been found for the condition. Radiographs, tomograms, and barium studies of the œsophagus were normal, and treatment produced no change in his condition. All laboratory tests were negative.

In September, venograms revealed that the superior cava was almost completely occluded, but that the innominate veins were patent. A moderate collateral circulation was present.

Because the patient complained a lot of his headaches and because the obstruction appeared to be localized, mediastinotomy was advised and done on October 15, 1957. A vertical medial sternal split gave good access and exposed a rather large stony hard mass of white tissue surrounding the superior cava between its origin and the right azygos vein. The latter was just free. The mass was about the size and shape of a flat orange. It felt and looked like a malignant growth. The right lung was normal and no pathological lymph-glands could be seen or felt in the hilum or in the mediastinum. Histologically this tissue was: "active fibrous tissue infiltrated with chronic inflammatory cells. It could possibly have been atrophied and fibrous thymic tissue." There was no evidence of past or present tuberculosis.

As the obstruction could not be taken away a by-pass was inserted from the side of the left innominate vein to the wall of the left atrium (not to the auricular appendage). The graft was a suitable length of the right femoral vein removed from the patient at the same operation. When the femoral vein had been taken out it contracted so much that it seemed little larger in lumen than a diary pencil. Nevertheless, after suturing, it functioned as a by-pass.

Convalescence was uneventful, but on the tenth post-operative day the right jugular vein was clinically thrombosed, and it became obvious from then onwards that the operation was a failure.

Nine months later the patient's clinical condition is unchanged and he is back at work despite his symptoms.

Comment.—The disappointing thing about this operation was the smallness of the lumen of the femoral vein after excision from the leg. It might have been a good plan to have put it into a papaverine solution before suturing it in place as a graft. The possibility of taking the other femoral vein and of cutting both open and then sewing them together as one tube, was considered, but rejected because it was felt that the suture lines, being increased in length, would favour thrombosis in the graft. This manœuvre has been tried experimentally and has not succeeded.

SUMMARY

Idiopathic mediastinal fibrosis is described as a clinical and a pathological entity. It is possible that some cases having the same signs and symptoms are due to mediastinal tuberculosis, syphilis, or a similar disease; but the lesions here described were idiopathic.

It is suggested that the pathological changes are akin to those found in 'periureteric fibrosis', 'pseudotumour of the orbit', and possibly to Reidel's disease in the thyroid gland.

Idiopathic mediastinal fibrosis is a self-limiting disease, in which the signs and symptoms of superior caval obstruction are replaced and mitigated by those associated with the growth of a collateral venous circulation. The disease seldom kills, it is compatible with a long life in which the patient can work, albeit at a disadvantage, with his fellows.

There is no medical treatment. Radiotherapy is of no avail, and surgical operations have proved to be almost uniformly unsuccessful. The failure of by-pass and replacement grafts is due to thrombosis in the grafts, and at the moment it seems to be impossible to prevent this. It should not be beyond the wit of surgeons eventually to cure this condition symptomatically: this cannot be done, except sporadically, at the present time.

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A SARCOMA INVOLVING THE JAWS IN AFRICAN CHILDREN

By DENIS BURKITT

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MALIGNANT tumours of the jaws in children, primary or secondary, are generally regarded as rare. A sarcoma involving the jaws in African children has recently come to be recognized at Mulago Hospital as a distinctive clinical condition and certainly the commonest malignancy of childhood.

Thirty-eight patients with this sarcoma in the jaws have been seen during the past 7 years; 32 of them were seen at Mulago Hospital and 6 at district hospitals. The tumour was diagnosed clinically in a further 8 children, but these have not been included in this series owing to lack of histological confirmation.

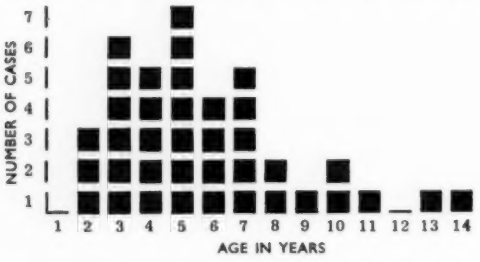

FIG. 246.—Showing age distribution in 38 cases.

Records of only 3 cases of this type of jaw sarcoma in children have been traced in the literature (Christiansen, 1938; Salmon and Darlington, 1944; Burford, Ackerman, and Robinson, 1944). Gelfand (1957) published an illustration of a sarcoma of the jaw in an African child without clinical details.

GEOGRAPHICAL DISTRIBUTION

Patients have not been limited to any particular area in Uganda, and have represented 11 different tribes. This sarcoma has also been observed in Kenya (Clifford, 1958), Tanganyika (Morris, 1958; Blackman, 1958), Nigeria (Thomas, 1958), the Belgian Congo (Thijs, 1958), and Southern Rhodesia (Gelfand, 1957). Patients with this syndrome have not yet been recognized in Johannesburg (Oettlé, 1958), Khartoum (Taylor, 1958), Lusaka (Buck, 1958), or Lourenço Marques (Prates, 1958).

CLINICAL FEATURES

These patients were from 2 to 14 years of age, 30 being between the ages of 2 and 7 years (*Fig.* 246).

In most cases the tumour started in the region of the alveolar process of a maxilla (*Fig.* 247) or the mandible (*Fig.* 249). Loosening of the deciduous molars was often the first symptom, the teeth in the involved area soon becoming embedded in tumour tissue only, and losing their insertion in bone. The next stage was irregular displacement of the teeth prior to their falling out. The tumour grew rapidly,

FIG. 247.—Sarcoma involving the left maxilla and arising in relation to the teeth. *Case* 1, taken 2 months after onset of symptoms.

grossly distorting the face. In only one patient (*Case* 20) did it ulcerate through the skin. Œdema of the eyelids and chemosis of the conjunctivæ indicated invasion of the orbit, and if the patient survived the eye became proptosed and finally destroyed. Less commonly the tumour presented as a swelling high in the maxilla with early invasion of the orbit (*Fig.* 248). Pain was not usually as severe as would have been expected from the appearance of the tumour. Within two or three months of onset of symptoms their relatives removed the majority of the children from hospital in a moribund condition.

Unless secondary infection occurred, which was not usual, the regional lymph-nodes were not

enlarged. Except for mild anæmia there were no characteristic changes in the blood-picture. Bence Jones proteose was not found in the urine.

A single quadrant of the jaws was clinically affected 20 times—the maxilla 14, and the mandible 6 (*Tables I–III* ; *Figs.* 247–249). In the remaining 18 patients two or more quadrants were clinically affected. The maxilla and the mandible of the same side were involved in 8 patients (*Table IV*; *Fig.* 250), both maxillæ in 4 (*Table V*; *Fig.* 251), and all four quadrants in 6 (*Table VI*; *Fig.* 252).

Radiographs frequently showed early tumour formation in quadrants not clinically involved. The lesions were osteolytic and were usually seen first in the region of the alveolar process (*Figs.* 253, 254).

FIG. 248.—*Case* 13. Sarcoma involving the right maxilla and extending into the orbit, but not arising in relation to the teeth.

Table I.—NINE PATIENTS WITH CLINICAL INVOLVEMENT OF ONE MAXILLA, THE TUMOUR ARISING IN RELATION TO THE ALVEOLAR PROCESS

CASE NO.	SEX	AGE (YEARS)	MAXILLA INVOLVED	OTHER DEPOSITS
1	M.	6	Left	None detected
2	M.	5	Right	At autopsy multiple deposits were found in both kidneys
3	M.	7	Right	At autopsy multiple deposits in both kidneys and liver. Tumour was also present in both adrenals and stomach
4	M.	7	Left	Rapidly increasing enlargement of the liver
5	F.	5	Left	None detected
6	M.	5	Left	None detected
7	M.	4	Right	None detected
8	M.	3	Left	Large retroperitoneal mass left side of abdomen
9	F.	5	Left	None detected

DEPOSITS OTHER THAN IN THE JAWS

These were demonstrated or strongly suspected in 15 patients. In this series the organs most frequently involved were the adrenals, the kidneys (*Fig.* 257), and the liver. Deposits have also been found in the thyroid, testis, heart, stomach, pancreas, a salivary gland, cranium, and femur. Deposits have not been demonstrated in the lymph-nodes or spleen. The detailed distribution of these deposits will be found in *Tables I–VI.* Specimens from an autopsy performed in Tanganyika (Morris, 1958) were sent here for examination. This child has a sarcoma of the mandible, and tumour deposits were found in both adrenals, both kidneys, liver, gall-bladder, urinary bladder, and stomach.

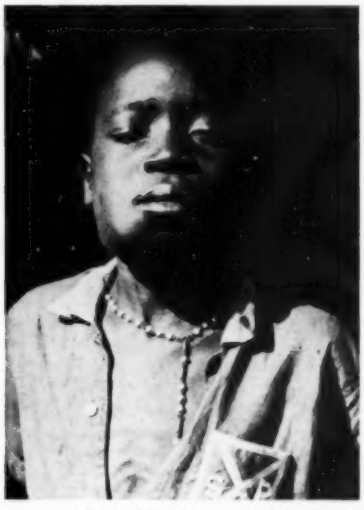

FIG. 249.—Sarcoma involving one mandible only. *Case* 18, taken 8 weeks after the appearance of the jaw tumour. This boy first reported to hospital with a large abdominal tumour in July, 1957. He had complained of abdominal pains since March, 1957. In January, 1958, he reported with a tumour involving the right side of his mandible, and loosening of the related teeth. At laparotomy a large tumour mass was found between the kidneys and invading both. The liver also contained numerous deposits. The histology of the liver and jaw tumours was identical.

Table II.— FIVE PATIENTS WITH CLINICAL INVOLVEMENT OF ONE MAXILLA, AND EARLY INVASION OF THE ORBIT

CASE NO.	SEX	AGE (YEARS)	MAXILLA INVOLVED	OTHER DEPOSITS
10	F.	6	Left	None detected
11	M.	3	Right	None detected
12	M.	2	Right	None detected
13	M.	10	Right	None detected
14	M.	14	Right	None detected

HISTOLOGY

Professor J. N. P. Davies has submitted the following description of the tumour histology: "The tumours are of a highly malignant type with very numerous and often atypical mitoses. The malignant cell is rounded or polyhedral, of variable size, with a large open vesicular nucleus, usually showing two prominent nucleoli. The cytoplasm is scanty and mildly eosinophilic. These cells occur singly or in clusters, often in rounded, otherwise clear spaces surrounded by masses of small, dark, round cells with dark compact hyperchromatic nuclei and scanty cytoplasm and strongly resembling lymphocytes; in some cases the tumour resembles a lymphosarcoma. In others these latter cells are less apparent and they appear to be degenerating. Degeneration, hæmorrhage, and necrosis are common. Small tumour giant cells are seen, in many cases resembling those seen in Hodgkin's disease. Rosettes, pseudo-rosettes, and neurofibrils are not seen, but some tumours have rounded spaces, sometimes optically empty, which bear some resemblance to rosettes, but others of these are occupied by the pale proliferating cells with the open vesicular nuclei."

FIG. 250.—Sarcoma involving the right maxilla and mandible. *Case* 25, taken 8 weeks after the appearance of the tumour.

FIG. 251.—Sarcoma involving both maxillæ. *Case* 30, taken 7 weeks after the appearance of the tumour. The deposit seen in the left frontal region had been noticed for one week. This patient died at home 3 months after the onset of symptoms.

FIG. 252.—Sarcoma involving all four quadrants of the jaws. *Case* 35, taken 8 weeks after the appearance of the tumour.

Table III.—SIX PATIENTS WITH CLINICAL INVOLVEMENT OF ONE SIDE OF THE MANDIBLE

CASE NO.	SEX	AGE (YEARS)	SIDE INVOLVED	OTHER DEPOSITS
15	M.	10	Left	At autopsy deposits were found in both adrenals, both kidneys, the pancreas, and the heart
16	M.	3	Left	None detected
17	M.	13	Left	None detected
18	M.	11	Right	Gross enlargement of the liver was detected clinically. At laparotomy there was a large tumour mass between the kidneys and involving both. The liver tumour was confirmed histologically
19	F.	6	Left	Thyroid (histological confirmation). Left kidney (observed at laparotomy)
20	F.	8	Left	At autopsy, multiple tumour deposits were seen in the liver

TREATMENT

Several years ago it was the practice to carry out radical operation when this appeared feasible. The tumour had recurred in the only patient who was traced, and operation is no longer advised. Radiotherapy has not been available. In 2 cases nitrogen mustard given intravenously in maximum doses led to temporary regression of the growths.

FIG. 253.—*Case* 22. Radiograph showing osteolytic changes in the mandible and displaced teeth.

FIG. 254.—*Case* 24. Radiograph showing displaced teeth and tumour eroding through the inferior margin of the mandible.

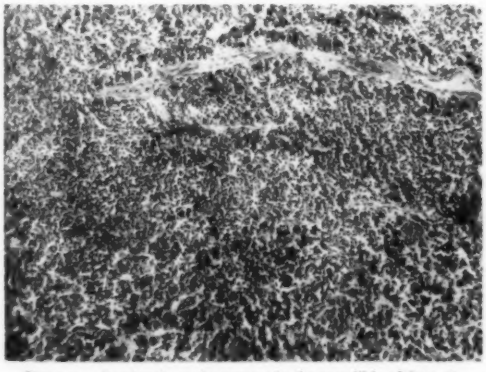

FIG. 255.—Section from the tumour in the mandible of *Case* 18. (× 50.)

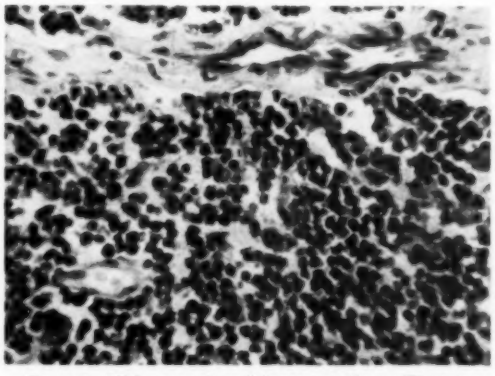

FIG. 256.—High-power view of the same section as *Fig.* 255. (× 200.)

DISCUSSION

Although the clinical picture of this sarcoma is easily recognized, its site of origin and nature remain obscure.

It is unlikely to be a primary jaw tumour with metastases. If the original tumour was a single primary it would require a mode of spread to other jaw quadrants which is not known to exist. This difficulty disappears if multiple primary tumours in the jaws are postulated. In either case, however, the pattern of metastases elsewhere, mainly to the contents of the abdomen, again involves a manner of spread quite unlike that of any known tumour.

Furthermore, in one patient in this series (*Case* 18) the abdominal tumour preceded the appearance of the jaw tumour by at least 6 months. In another (*Case* 38) a tumour in the testis was observed first. This was followed by an abdominal tumour, and loosening of the teeth. At autopsy both kidneys and adrenals were found grossly involved in tumour (*Fig.* 257), and deposits were demonstrated in the jaws.

The primary growth might be abdominal, the tumours in the jaws metastatic. If so, the condition

must have been present within the abdomen in every case, although in many instances clinical evidence was lacking. It is significant that all the 6 cases coming to autopsy, and both cases coming to laparotomy, were found to have intra-abdominal deposits, although in only one of them (*Case* 18) had they been suspected during life.

The other possibility is that multiple primaries appear independently in jaws or abdomen, or both. An abdominal sarcoma of similar histology, occurring in the same age-group but without involvement of the jaws, is not rare at Mulago Hospital. During the past 5½ years a tumour of this type has been found 9 times at autopsy, and a further 8 cases have been confirmed by biopsy. Moreover, in these patients tumour deposits have been observed in every structure found involved in association with a jaw sarcoma, the adrenals, kidneys, and liver being predominantly affected.

It is not the intention of this paper to speculate on the exact nature of the sarcoma. Neuroblastoma has naturally been considered in view of the distribution of the tumour in the adrenals, liver, and skull, but there is no definite histological support for this diagnosis. It seems possible that it will eventually be identified as a reticulosarcoma, although deposits in

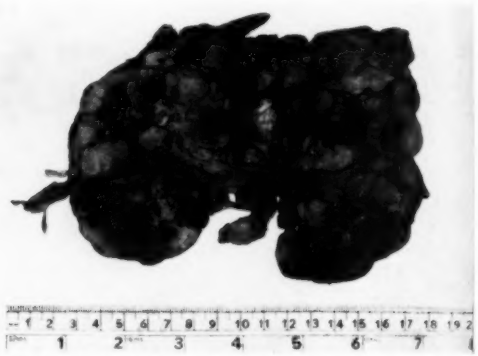

FIG. 257.—*Case* 38. Kidneys and adrenals from a case with tumour deposits in all four quadrants of the jaws. A boy aged 7 years was admitted to hospital in a moribund condition. A month previously a tumour in the left testis had been observed and shortly afterwards an abdominal mass noticed. On admission the teeth in all four quadrants of the jaw were found to be loose. There was a hard swelling in the right side of the thyroid, and another in the left testis. A large fixed mass filled much of the upper abdomen. Both eyes were proptosed, and there was a divergent squint. X-ray examination confirmed tumour deposits in both maxillæ and both mandibles. The patient died one week after admission. At autopsy tumour deposits were found in both kidneys, both adrenals, heart, stomach, thyroid, left testis, and right submaxillary salivary gland.

Table IV.—EIGHT PATIENTS WITH CLINICAL INVOLVEMENT OF THE MAXILLA AND MANDIBLE ON THE SAME SIDE

CASE NO.	SEX	AGE (YEARS)	SIDE INVOLVED	OTHER DEPOSITS
21	F.	6	Right	At autopsy tumour deposits were found in both adrenals
22	M.	7	Left	None detected
23	F.	2	Left	None detected
24	M.	4	Right	None detected
25	M.	2	Right	Ill-defined mass right side of abdomen
26	F.	3	Right	Hard mobile mass in lower abdomen
27	M.	5	Left	None detected
28	M.	9	Left	None detected

Table V.—FOUR PATIENTS WITH CLINICAL INVOLVEMENT OF BOTH MAXILLÆ

CASE NO.	SEX	AGE (YEARS)	OTHER DEPOSITS
29	F.	7	None detected
30	M.	4	Tumour in left frontal region with radiological evidence of bone involvement
31	M.	3	None detected
32	F.	8	None detected

Table VI.—SIX PATIENTS WITH CLINICAL INVOLVEMENT OF ALL FOUR JAW QUADRANTS

CASE NO.	SEX	AGE (YEARS)	OTHER DEPOSITS
33	M.	4	None detected
34	M.	4	None detected
35	M.	3	Tumour in left testis (confirmed histologically)
36	M.	5	None detected
37	M.	5	Hard fixed mass in epigastrium. Deposit in shaft of left femur found on X-ray examination
38	M.	7	Tumours in the left testis, thyroid, and abdomen were detected clinically. At autopsy there were deposits in both kidneys, both adrenals, stomach, heart, and salivary glands

the lymph-glands and spleen, which would be expected in this group of tumours, have not been observed. The age-incidence and anatomical distribution of deposits differ from previous descriptions of reticulosarcomata. It may well be that we have in Uganda a syndrome of diverse characteristics and that this series of jaw sarcomata is no more than a group which has attracted attention owing to its very striking clinical features. Still less is it intended to speculate as to why this sarcoma should occur so frequently here. So far no common factor has been recognized which might have a bearing on the aetiology.

SUMMARY

Thirty-eight cases of a sarcoma involving the jaws of African children are described. This is a syndrome which has not previously been fully recognized. It is by far the commonest malignant tumour of childhood seen at Mulago Hospital.

Acknowledgements.—I am indebted to J. N. P. Davies, Professor of Pathology at Makerere College Medical School, for his help in endeavouring to determine the nature of this tumour. I would like to acknowledge with gratitude the help and encouragement I have received from H. J. Croot, Professor of Surgery, and my surgical colleagues. I would also like to thank Dr. A. G. M. Davies, Specialist Radiologist, Peter Cull, Medical Illustrator, and the staffs of the Cancer Registry and Photographic Department at the Medical School. I am grateful to the Director of Medical Services, Uganda, for permission to publish this paper.

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CAVERNOUS HÆMANGIOMA OF THE DESCENDING COLON

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SOLITARY cavernous hæmangioma of the large bowel is a rare condition. The first recorded hæmangioma of the gastro-intestinal tract was by Phillips in 1839, when he reported a case with a capillary hæmangioma of the rectum. In a collective review of all types of hæmangiomatous malformations of the gastro-intestinal tract by Gentry, Dockerty, and Clagett in 1949, only 4 cases out of their series of 189 represented the solitary cavernous hæmangioma in the colon (cæcum to rectosigmoid junction). Holman (1948) reported a case of a solitary diffuse hæmangioma of the sigmoid colon, presenting with rectal bleeding and anæmia, successfully treated by surgery.

The case presented here is a solitary cavernous hæmangioma of the descending colon, which was successfully treated by surgery.

CASE REPORT

A Jamaican male, aged 26, was admitted to the London Hospital in May, 1956, complaining of abdominal pain. In the late evening, thirteen hours before his admission to hospital, he developed central colicky abdominal pain. This pain continued for one hour until he had his bowels open, after which he experienced some relief. He noticed that mixed with his stools were numerous bright red clots of blood. No mucus or slime was seen.

Soon after going to bed he was awakened with further abdominal pain and nausea. After vomiting a cupful of clear fluid he felt a little better, but continued to have abdominal pain up till the time of his admission.

He denied previous history of abdominal pain or bleeding per rectum.

ON EXAMINATION.—The temperature, pulse, and respiration were all normal. No hæmangioma was seen on the skin or mucous membranes. The tongue was clean and moist, fetor oris was not detected. The cardio-vascular, respiratory, and central nervous systems were all normal, and routine urine analysis showed no abnormality.

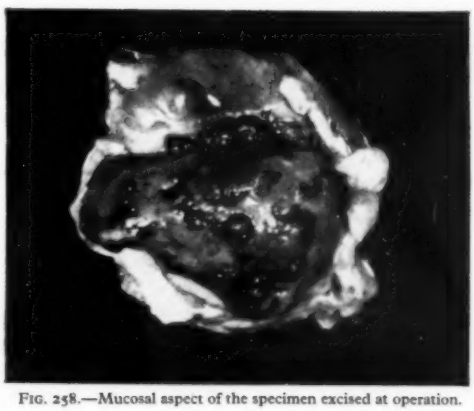

FIG. 258.—Mucosal aspect of the specimen excised at operation.

The abdomen was not distended and moved well on respiration. Peristalsis was not seen. Tenderness was present in both iliac fossæ and a firm, tender, mobile mass the size of a tennis ball was felt in the left iliac fossa.

Bowel-sounds were not increased.

On rectal examination a small quantity of fresh blood was seen on the fingercot, otherwise nothing was felt to be abnormal.

SPECIAL INVESTIGATIONS.—Hæmoglobin was 105 per cent, chest radiograph showed the lung fields to be clear.

A pre-operative diagnosis of intussusception of the descending colon was made and a laparotomy was performed.

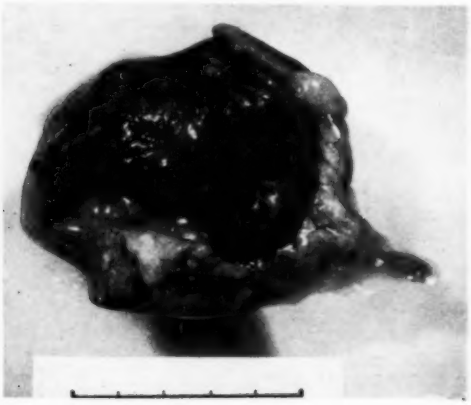

FIG. 259.—Serosal surface of the specimen.

AT OPERATION.—A laparotomy was performed under general anæsthesia, through a left paramedian incision, and an excess of clear serous fluid was seen in the peritoneal cavity. In the position of the mass felt on external examination was a large hæmangioma of the descending colon just proximal to the sigmoid loop (*Fig.* 258). The main mass of the tumour was on the peritoneal aspect of the colon, and measured 6 × 6 × 4 cm. Despite a search of the other contents of the abdominal cavity, no other hæmangioma was found. The colon was then mobilized and the tumour resected with a portion of normal adjoining bowel. An end-to-end anastomosis was performed, and through a separate stab wound a rubber drain was placed at the site of the anastomosis.

Post-operative progress was uneventful until the eighth day, when the patient complained of abdominal pain starting ten minutes after having his bowels open, followed by vomiting of bile-stained fluid. A naso-œsophageal tube was passed and the contents of the stomach aspirated hourly for twenty-four hours. Following this he remained quite well and was discharged home on the fourteenth post-operative day.

PATHOLOGICAL FINDINGS.—

Macroscopic Appearance.—An 8-cm. length of colon containing an ill-defined and slightly lobulated brown tumour (6 × 5 × 4·5 cm.). Most of the tumour projected outwards beneath the intact peritoneum, but it also projected into the lumen of the colon without any apparent ulceration of the mucosa (*Figs.* 259, 260).

Microscopic Appearance.—The tumour was a cavernous hæmangioma which extended from the mucosa to the serosa, with displacement and thinning of the muscular layer of the colon, and loss of the muscularis mucosæ. The angiomatous spaces appeared to be in continuity with the dilated capillaries of the lamina propria immediately over the tumour (*Fig.* 260). There was no evidence of malignant change.

FIG. 260.—Microscopic appearance of tumour on section. (× 5.)

SUMMARY

A solitary cavernous hæmangioma of the descending colon in a young man, successfully treated by a resection and end-to-end anastomosis is described, and the literature briefly reviewed.

Acknowledgements.—I wish to express my thanks to Mr. Alan Perry for his permission to publish this case, and to Professor Dorothy Russell and the staff of the Bernhard Baron Institute of Pathology for their help and advice.

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LIPOSARCOMA OF KIDNEY

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Of all the malignant tumours which arise in the kidney, liposarcoma must be among the rarest. A search of the literature has brought to light only 29 cases of the condition. We propose to analyse these cases, after first presenting one of our own which stimulated this review.

CASE REPORT

A man, aged 39 years, was admitted as an emergency to the Whittington Hospital under the care of one of us (P.T.S.), with a 3-day history of severe pain under the right costal margin which radiated through to the back and into the right shoulder. At times he had exacerbations of pain amounting to colic. He had vomited on three occasions. There was no history of hæmaturia, frequency, or dysuria. There was no history of any past illness.

On Examination.—An obese, barrel-chested man with a slightly furred tongue, temperature 102° F., pulse 96. The cardiovascular and respiratory systems were normal except for slightly diminished air entry at the right base. The abdomen showed considerable tenderness and some rigidity in the right hypochondrium. The right kidney was not palpable and there was no tenderness in the right loin. Examination of the urine showed no abnormality.

The leucocyte count was 13,000, 69 per cent polymorphs. Radiographic examination of the abdomen, erect and supine, showed no abnormality.

A provisional diagnosis of acute cholecystitis was made and the patient was given a short course of penicillin and streptomycin. His symptoms and signs rapidly regressed. He was then further investigated.

Cholecystography showed a normally functioning gall-bladder and no evidence of gall-stones.

An intravenous pyelogram showed good excretion from the left kidney and a grossly abnormal picture on the right (*Fig.* 261).

A right retrograde pyelogram showed gross clubbing and elongation of the upper and middle calices; stereoscopic views showed these calices to be spread out around a space-occupying lesion in the kidney (*Fig.* 262).

Aortography to elucidate the nature of the right renal lesion further was carried out following the technique described by Whiteside (1953). The first film taken in the early arterial phase (*Fig.* 263) shows a normal left renal artery and branches. The right renal artery is much larger than the left, as are its branches. The second film (*Fig.* 264) shows the early nephrogram phase. The right kidney is three times the size of the left, and there is pooling of dye in the upper pole, similar to that seen in Grawitz adenocarcinoma.

As a chest radiograph showed no pulmonary metastases right nephrectomy was advised.

At Operation (P. T. S.).—The right kidney was explored, using a standard incision through the bed of the twelfth rib. The kidney, together with its perinephric fat, was firmly fixed to the psoas and quadratus lumborum muscles, and to the peritoneum and inferior vena cava. After enlarging the incision forward, opening the peritoneum, and resecting most of the eleventh rib, a good exposure was obtained.

The kidney was mobilized with some difficulty from its bed and dissected off the inferior vena cava. The renal vein, represented by two short trunks ½ in. long and

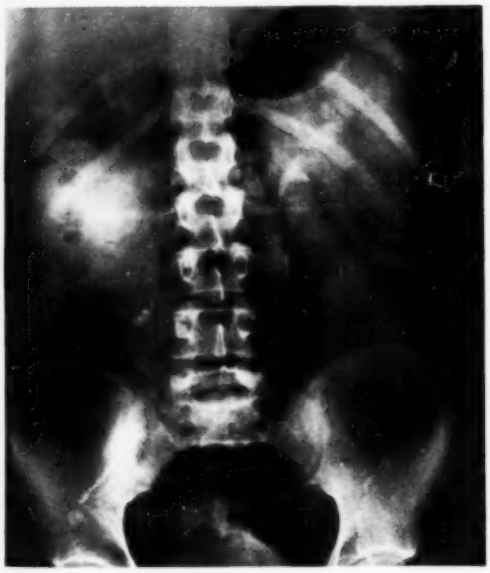

Fig. 261.—Intravenous pyelogram showing a grossly abnormal right kidney.

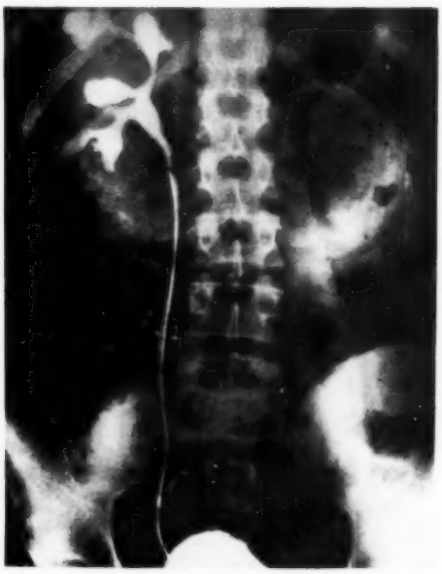

Fig. 262.—Right retrograde pyelogram showing clubbing and elongation of upper and middle calices which are spread out around a space-occupying lesion of the right kidney.

FIG. 263.—Aortogram, arterial phase, showing enlarged right renal artery and branches.

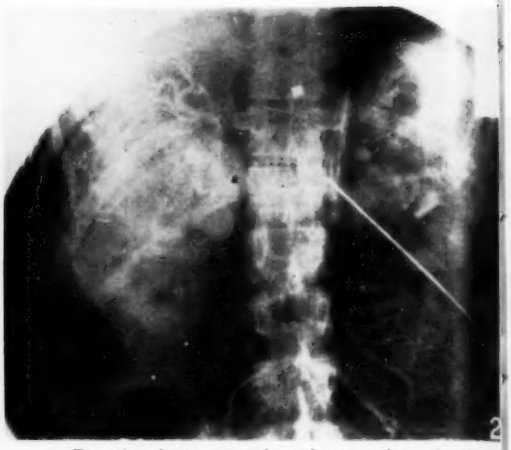

FIG. 264.—Aortogram, early nephrogram phase, showing pooling of dye in right kidney, suggestive of Grawitz adenocarcinoma.

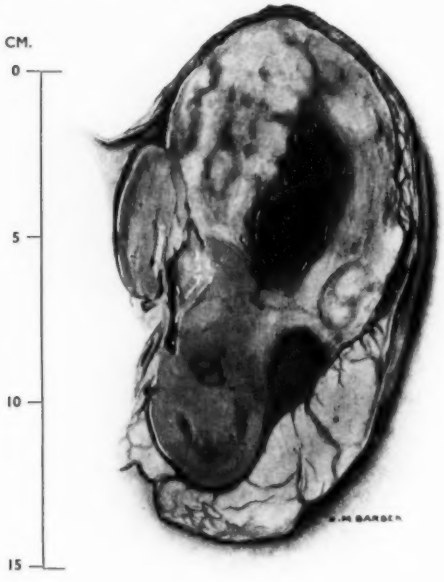

FIG. 265.—One-half of nephrectomy specimen, showing replacement of upper part of kidney by mottled yellow and grey tumour tissue with areas of hæmorrhage into it. The diaphragm is seen adherent to the upper part of the specimen. (× ⅔.)

½ in. wide, were divided without mishap, and the rest of the renal pedicle gave no further trouble. The upper pole of the kidney was then found to be firmly adherent to the diaphragm posteriorly, a piece of which measuring 7·5 × 12·5 cm. was removed, together with the kidney. The right suprarenal gland was never identified.

The chest was closed by suturing the diaphragm to the parietal pleura at a much higher level, thus obliterating the costophrenic angle posteriorly. The incision was closed around a tube-drain with an underwater seal.

Air and fluid were aspirated from the right chest on five occasions during the first post-operative week. After this the right lung remained expanded and further convalescence was uneventful.

The specimen (*Fig.* 265) measures 18 × 10 × 10 cm. The greater part of the kidney substance was replaced by mottled yellow and grey friable tumour tissue, with several large areas of hæmorrhage. At the upper pole tumour appears to have spread through the capsule and to be continuous with the perinephric fat, which it closely resembles to the naked eye. Histologically, the tumour consists mainly of well-differentiated fat cells with scattered clumps of polygonal cells, characteristic of liposarcoma of low-grade malignancy (*Figs.* 266, 267).

The patient was alive, well, and clinically free from recurrence when last seen two and a half years after his operation.

REVIEW OF CASES

Judd and Donald (1932) reviewed renal tumours over a 30-year period at the Mayo Clinic, and out of 20 sarcomata found only 1 liposarcoma. The first case was described by Nuernberg in 1904, but he gives no clinical details and only a brief description of the pathology. Hartwig fully described a case in 1907. Since that time the condition has been reported sporadically.

An interesting feature is the association (in 10 of the 29 recorded cases) of renal liposarcoma with the condition of tuberous sclerosis. This association was first recorded by Vogt in 1908, and a review of the renal lesions in 58 cases of tuberous sclerosis was published by Fischer in 1911. In 1942 Merz found renal tumours in 36 out of 42 cases of tuberous sclerosis.

The condition of tuberous sclerosis was first described by Bourneville in 1880. There have been numerous accounts since in the English language, notably those of Critchley and Earl (1932) and of Moolten (1942). Pathologically there occurs a hypertrophic nodular gliosis within the brain. There may be associated rhabdomyomata of the heart, retinal phacoma, adenoma sebaceum of the face (typically of butterfly distribution), and renal neoplasm. The associated lesions vary in combination and number.

The condition shows a marked familio-hereditary tendency. The cerebral changes produce mental deficiency and epilepsy. Facial adenoma sebaceum is invariably present at puberty.

Hyman (1922) states that renal tumours are present in 80 per cent of cases; usually they are multiple and bilateral and consist of primitive

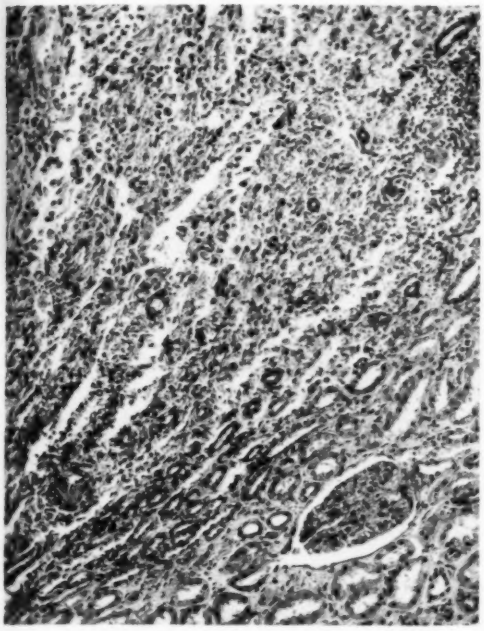

FIG. 266.—Liposarcoma of kidney showing infiltration of kidney by tumour tissue. (× 100.)

mesenchymal elements. Thus angiomata, fibromata, endotheliomata, myomata, lipomata, or combinations of these have been noted, according to the predominant tissue. Malignant change in these tumours seems to be rare, and when it occurs metastasis is very uncommon. But since many of these patients die of the cerebral manifestations before they reach the age of 20 years, the renal lesions remain occult and it is possible that malignant change in them would have supervened later. However, the renal tumours can cause symptoms in this condition and they therefore interest the urologist.

Hulse and Palik in 1951 collected 130 cases in which the diagnosis of tuberous sclerosis had been made ante mortem. They give a valuable bibliography. They discuss the presence of renal hamartoma. This term was introduced by Albrecht (1904). It implies dysplasia as opposed to neoplasia; a defect in tissue combination. If we subscribe to this term we may perhaps place renal liposarcoma at its 'malignant fringe', for the association of renal liposarcoma with a generalized defect of tissue combination—what Moolten (1942) terms a hamartiosis, in fact with tuberous sclerosis, is well established. Moolten goes on to suggest that the defect in induction by embryonic organizers may in some, and perhaps in the same way, be responsible for the malignant change. On the other hand, renal liposarcoma can occur without the changes of tuberous sclerosis, and such cases are reported. Dos Santos (1942) has suggested that the isolated renal lesion represents a *forme fruste* of the full syndrome. It is interesting that a large renal tumour may be

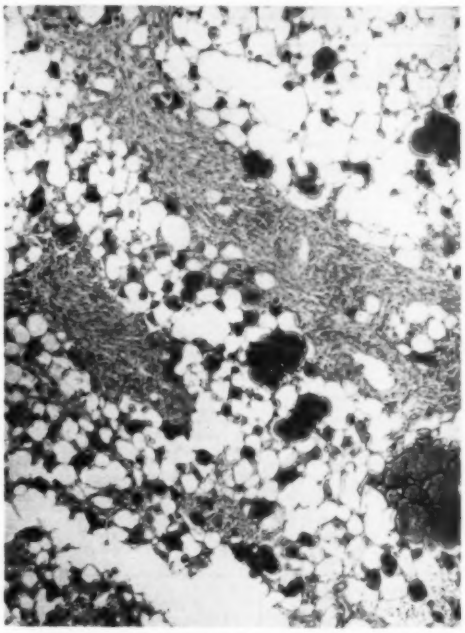

FIG. 267.—Liposarcoma of kidney showing well differentiated fat cells, with scattered clumps of polygonal cells. (× 54.)

associated with minimal evidence of tuberous sclerosis in the form of adenoma sebaceum, as in Melicow's (1944) case. There is certainly some connexion between renal abnormalities of this sort and generalized defects of tissue combination. For instance, renal tumours have been noted with von Recklinghausen's disease and with von Hippel's type of angiomatosis. There is little doubt, however, that in 19 of the reported cases, liposarcoma of the kidney occurred without any evidence of tuberous sclerosis.

The clinical and pathological features of what we believe to be all the recorded cases of renal liposarcoma are set out in the accompanying table (*Table I*), but cases of liposarcoma obviously arising in the perinephric fat have been excluded. From this certain facts emerge. There is no significant sex preponderance. This is in accordance with Stout's (1949) findings, who, in an analysis of liposarcoma in all regions, points out that its incidence is equal between the sexes, as opposed to the benign lipoma, 73 per cent of which occur in women. Nearly half the cases occurred in the fourth decade; the remainder were evenly distributed between the ages of 10 and 75 years (*Fig.* 268).

Table I.—CLINICAL AND PATHOLOGICAL F... RECORDE...

AUTHOR AND YEAR	AGE AND SEX	PRESENTING SYMPTOMS	PAIN	HÆMATURIA	PHYSICAL SIGNS	ASSOCIATED CONDITIONS	INVESTI...
Nuernberg, 1904	50, F.	No details					
Hartwig, 1907	36, F.	Progressive abdominal enlargement, 8 yr. Pain and collapse following trauma	+	−			
Vogt, 1908	37, F.	Generalized œdema. Mentally backward		−	Died in cardiac failure	Adenoma sebaceum	
	14, M.	Epilepsy. Mentally backward		−	Died in renal failure	Adenoma sebaceum	
1910	15, M.	No details			Died of tuberculosis	Adenoma sebaceum	
Fischer, 1911	16, M.	Epilepsy. Mental defective		−	Died in epileptic attack	Adenoma sebaceum	
Harbitz, 1912	38, F.	Swelling in right lower abdomen, 3 yr. Epileptic	+	−	Tumour from right costal margin to right iliac fossa. Smaller tumour left loin	Adenoma sebaceum	
Korner and Kirch-Hertel, 1923	67, M.	Cardiac failure		−	No symptoms or signs of tuberous sclerosis	Auricular fibrillation and congestive cardiac failure	
Lubarsch, 1925	62, F.	No details					
McCartney and Wynne, 1936	37, F.	Aching pain in right loin, 6 wk. Severe loin pain, 3 hr.	+	−	Tender mass in right loin		poor exc... ...ng pyelog... ...ey and ure...
Becker, 1936	31, F.	Increasing swelling of abdomen and lassitude, 4 yr.		−	Large right renal mass	4 months pregnant	...l insufflat... ...rade
Froug, 1941	30, F.	Loss of energy, 3 mth. Left-sided abdominal swelling, 1 mth.		−	Mass extending from left costal margin to below iliac crest	Adenoma sebaceum. Epilepsy. Low mentality	...displacemen...
Pearse, 1942	53, F.	Lump in left hypochondrium, 2 yr.		−			...arge left ki...
	35, F.	Pain in left loin (duration not stated)	+	−	None	Left ureteric calculus	...stone in l... ...twice norr...
Dos Santos and Wohlwill, 1942	31, F.	Anorexia. Loss of weight. Pain in left loin	+	+	Enormous left kidney	Congenital cystic disease of lungs (bronchitis since infancy)	...gn, bilater... ...pooling, ...
Weisel, Dockerty, and Priestley, 1943	68, M.	Weakness and loss of weight. Colicky left-sided abdominal pain, 6 mth.	+	−	Large left abdominal mass		
Melicow, 1944	24, F.	Pain in right flank. Loss of weight. Observed 4 yr.	+	−		Adenoma sebaceum	? polycysti...
	73, F.	Pain in left side of abdomen	+	−		Diverticulitis of colon	...oor excre... ...r outline
Fish and McLaughlin, 1946	24, F.	Loss of energy, anorexia. Abdominal pain, 1 yr. Recurrent fever and anæmia	+	−	Large mass in right loin	Adenoma sebaceum. Neurofibromatosis	...er cent. ... ...sis
Wagner, 1946	40, M.	Large mass in right loin, 6 yr.					...wer pole t... ...as in hypo...
Tesler and Koiransky, 1947	67, M.	Anorexia and weakness, 5 wk.	−	−	Generalized wasting	Left nephrolithiasis and hydronephrosis	...nephrolithi... ...sis
Newman and Reed, 1949	37, M.	Severe pain right loin, 2 d.	+	−	Tender right loin, and pain on flexing right hip. No mass		...id retrogra...
Edelman, 1951	46, F.	Accidental finding of mass in left upper abdomen at routine examination. Painless hæmaturia of 48 hr. duration occurred 1 mth. before	−	+	Tumour in left loin		...deformity ... ...calices
	40, F.	Left lower abdominal pain, 2 d.	+	−			...nd retrogr... ...outline with
Schulte, 1951	51, F.	Pain in right loin, 1 yr.	+	−	None, other than tenderness over McBurney's point		...id retrogra... ...right renal
Brady and Wayburn, 1951	36, F.	Pain and mass in left flank, 3 yr.	+	−	Tender tumour in left loin		...ncoplasm o...
Hulse and Palik, 1951	42, F.	Faintness, pallor, and pain, 4 d.	+	−	Large renal tumour	Tuberous sclerosis diagnosed radiologically. Hereditary element. Subungual hamartoma	...mass in low...
Mogg, 1957	27, F.	Large right renal mass discovered incidentally. Had caused no discomfort	−	−		Chronis cervicitis	...poor excr... ...aliceal dist...
Williams and Savage, 1958	39, M.	Right subcostal pain and vomiting, 3 d.	+	−	Tender right hypochondrium. No mass. Temperature, 102° F.		...retrograde ... ...calical ... ...arge right ... ...denocarcin...

...P.—Intrav...

RECORDED CASES OF LIPOSARCOMA OF KIDNEY

ED ONS	INVESTIGATIONS	TREATMENT	PATHOLOGY	FOLLOW-UP
		Right nephrectomy	Large whitish-yellow growth	Not reported
		Right nephrectomy	Kidney 3500 g. 23 × 17 × 16 cm. Numerous nodules	Died 2nd post-operative day (hæmorrhage)
ceum			Post-mortem, bilateral multiple necrotic yellow tumours	
ceum			Post-mortem, bilateral multiple necrotic hæmorrhagic yellow tumours	
ceum			Post-mortem, growth confined to kidney	
ceum			Post-mortem, numerous small (1 cm.) yellow tumours	
ceum		Biopsy of right renal tumour	Post-mortem, multiple bilateral tumours	Died 3rd post-operative day
lation and diac fail-			Post-mortem, right kidney, benign lipoma. Left kidney, multiple liposarcomata	
		Left nephrectomy	Multiple tumours	Not reported
	poor excretion right side. ing pyelogram, displacement ey and ureter	Right nephrectomy. Radiotherapy	Lobulated hæmorrhagic mass replacing lower pole	No sign of recurrence, but developed primary ovarian carcinoma 22 yr. later
nant	insufflation, I.V.P. and ular	Right nephrectomy. Radiotherapy	Kidney 3500 g. Upper pole compressed by growth	Septic abortion. Died 28th post-operative day
ceum. mental-	isplacement and distortion of	Left nephrectomy	Upper pole replaced by large encephaloid mass, 24 × 12 × 7 cm. Multiple nodules in parenchyma	Alive and well 1 yr. later
	arge left kidney	Left nephrectomy	Kidney 10 × 5 × 2·5 cm. Tumours in upper and lower poles	Not reported
alculus	tone in left ureter. Renal twice normal size	Left nephrectomy and ureterectomy. Radiotherapy	Kidney 15 × 10 × 6 cm. Compressed by tumour measuring 10 × 8 × 4 cm.	Alive and well 3½ yr. later
ic disease ronchitis	m, bilateral renal tumours. pooling, almost angiomatous	4 yr. observation. Left nephrectomy for increasing pain	Liposarcoma of left kidney. No other details recorded	Died of bronchopneumonia and pneumothorax 3 yr. later
		Left nephrectomy	Lipofibroma sarcoma of left kidney. No other details recorded	Alive and well 2 yr. later
ceum	polycystic disease	Right nephrectomy	Multiple hæmorrhagic nodules	Not reported
f colon	oor excretion on left, with outline	Left nephrectomy		Died of recurrence 88th post-operative day
ceum. tosis	er cent. I.V.P., right hydro-	3 yr. observation. Right nephrectomy	Kidney 1400 g. Multiple tumours	Alive and well 2 yr. later
	wer pole tumour. Aortogram, as in hypernephroma	Attempted removal (third)	Large liposarcoma, lower pole of right kidney	Died 2nd post-operative day
iasis and s	nephrolithiasis and hydro- sis	None	Tumour invading perinephric fat. 815 stones in dilated pelvis and ureter. Metastases in lungs and regional lymph-nodes	Died 5 wk. after admission
	nd retrograde pyelogram, filling	Right nephrectomy	Kidney 260 g. 15 × 9 × 6 cm. Largely replaced by growth	Alive and well 8 mth. later
	deformity of left upper and calices	Left nephrectomy	Kidney 11 × 6 × 3·5 cm. Multiple tumours. Papillary fragments in pelvis of ureter	Alive and well 9½ yr. later
	nd retrograde, indistinct left utline with distortion of upper	Left nephrectomy	Kidney 450 g. 20 × 10 × 6 cm. Single tumour of 12 cm. diameter. Locally invasive	Alive and well 3 yr. later
	d retrograde, indefinite filling ight renal pelvis	Exploratory laparotomy. Right nephrectomy 2 mth. later	Right kidney normal in size. One pole replaced by yellowish-grey neoplasm. Multiple nodules up to 0·5 c.m. diameter in rest of kidney	Alive and well 12 yr. later
	neoplasm of left kidney	Left nephrectomy. Radiotherapy	Kidney 16 × 10 × 7 cm. Largely replaced by soft friable tumour	Alive and well 6 yr. later
sis diag- gically. lement. martoma	mass in lower pole	Nephrectomy	Tumour 20 × 10 cm. Histologically benign, but renal capsule was penetrated by growth. "Hamartoma"	Alive and well 2½ yr. later
tis	poor excretion of right with caliceal distortion	Right nephrectomy	Specimen 1859 g. Kidney parenchyma a mere strip on the periphery	Alive and well 2 yr. later
	retrograde, right upper and caliceal distortion. Aorto- arge right kidney with pooling enocarcinoma	Right nephrectomy	Kidney 18 × 10 × 10 cm. Largely replaced by tumour which invaded capsule and diaphragm at upper pole	Alive and well 2½ yr. later

2.—Intravenous pyelogram.

The commonest presenting symptom was pain associated with a lump in one or other loin; frequently there was anorexia and loss of weight in addition, and sometimes fever. These symptoms were occasionally of several years' duration (Becker, 1936; Brady and Wayburn, 1951; Dos Santos, 1942). Hæmaturia was notable by its absence. It was present in only 2 of the cases and in 1 of these papillary fragments of tumour were found in the renal pelvis. In neither case was it a predominant symptom.

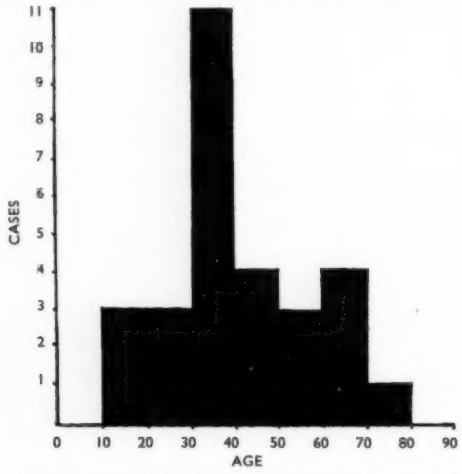

FIG. 268.—Age incidence of the 29 recorded cases of liposarcoma of kidney.

The pyelographic findings were simply those of a space-occupying lesion, with distortion and displacement of the pelvi-caliceal system. There were no special diagnostic features. Aortography was carried out in 3 of the cases and on each occasion showed pooling of dye suggestive of a vascular neoplasm.

Nephrectomy was carried out in 21 of the 29 cases. The operation often proved formidable; thus Wagner (1946) described a case in which two previous attempts had been made to remove a huge right kidney, the patient dying after a third unsuccessful attempt. Two of the cases took over three hours at operation and a third patient died from blood-loss after two hours. Our own case was no exception in regard to difficulty.

Pathologically, certain features emerge. Multiple tumours occurred in 12 out of the 29 cases. In 4 the condition was bilateral. The tumours were soft and vascular on section, and appeared to be locally invasive. Microscopically, oval cells with hyperchromatic nuclei and mitotic figures appeared in tightly packed strands between a variety of mesenchymal elements, as described earlier. Nuernberg stated that the cytoplasm stains poorly with van Gieson, unlike the benign tumour. The tumour cells are rich in fat. There is probably no difference in glycogen distribution between benign and malignant tumours. Spread via lymphatics and blood-stream is very rare, which accounts for the long periods of survival following extirpation. Only 2 cases showed evidence of lymphatic spread post mortem, and 1 of these had pleural metastases.

In 2 of the recorded cases (Pearse, 1942; Tesler and Koiransky, 1947) liposarcoma was associated with renal calculi. In the latter a tumour of the lower pole was associated with a pyonephrosis and there were 815 stones in the dilated pelvis and ureter. This patient died with metastases in lungs, pleura, and regional lymph-nodes. In the former case a tumour of the left kidney was associated with a stone in the upper third of the ureter of the same side.

Of the 21 cases submitted to nephrectomy, 2 died within 72 hours of operation and 1 died 28 days later from a septic abortion.

Of the 19 cases surviving nephrectomy, 1 died of recurrence on the 88th day and another 3 years later from unrelated causes. One was alive and well 8 months, and another 1 year, later. Five cases were alive and well 2 years, and two more 3 years, after nephrectomy. One was alive and well 6 years, another 9½ years, and another 12 years, after operation. One patient is still alive 23 years after nephrectomy, but developed a right ovarian carcinoma 22 years after, for which a very radical resection has been carried out (McCartney and Wynne, 1936). In 4 of the cases surviving nephrectomy no follow-up is reported. The outlook for those surviving nephrectomy is, therefore, reasonably good.

SUMMARY

A case of liposarcoma of the kidney is described and the literature reviewed. The condition is rare, and a third of the cases are associated with tuberous sclerosis.

The majority of cases present with renal swelling or pain in the affected loin. Hæmaturia is rare. The usual renal investigations, including aortography, suggest a vascular neoplasm. The diagnosis can only reasonably be made pre-operatively if there is evidence of tuberous sclerosis.

Nephrectomy should be performed, but may be difficult.

The value of post-operative radiotherapy is doubtful as these tumours are radio-resistant.

Acknowledgements.—We wish to express our thanks to Dr. S. H. G. Robinson of the Central Histological Laboratory, Whittington Hospital, for the report on the kidney; to Mr. G. W. Moore, Senior Technician, for the photomicrographs; and to Miss D. M. Barber for the coloured illustration of the specimen. Also to Miss Mason of the Photographic Department of St. James's Hospital, Balham, for the radiographs; and to Mr. H. Collinson for drawing *Fig.* 268.

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THE SIGNIFICANCE OF BIOPSY IN BLADDER TUMOURS

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DIVERGENT opinions have been expressed about the need to obtain a portion of the subjacent bladder muscle when a biopsy is carried out in cases of bladder tumour. Jewett (1947), discussing infiltrating carcinoma of the bladder, stated that the diagnosis is established in questionable cases by a properly taken biopsy specimen and that a good-sized piece of tissue, including some muscularis, should be removed in order to establish the presence or absence of infiltration. In contrast, Dukes (1955) stated that although pathologists are reluctant to describe any tumour as malignant on cytology alone without some evidence of invasion or infiltration, such a rule is too strict in the case of bladder tumours, though it may be a good rule for most other organs of the body. On the grounds of cytology alone, bladder tumours must sometimes be described as well-differentiated transitional cell carcinomas even in the absence of demonstrable infiltration. Dukes further stated that such policy brings pathological nomenclature into line with clinical experience because tumours may behave clinically as malignant growths even though no histological evidence of infiltration can be obtained: metastases have occurred in lymph-nodes or in other organs although microscopic examination of the primary tumour has failed to reveal evidence of infiltration.

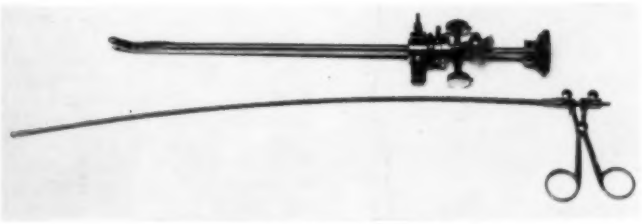


FIG. 269.—Riches cystoscope and crocodile forceps.

The following study was carried out in an attempt to resolve these conflicting opinions. The plan, in the main, was to compare the histology of a biopsy specimen, taken in a way which seldom provides deep tissue, with that of the bulk or whole of the tumour obtained either at operation or post mortem.

MATERIALS AND METHOD

Fifty-two patients with bladder tumours were studied. All the biopsies were performed under general anæsthesia and were carried out by the transurethral route. The majority were carried out by registrars in training and generally without prolonged urological experience. In 20 cases it was subsequently possible to compare the histology of the biopsy with that of the tumour; in 32 cases, however,

it was not possible to make the comparison because the eventual treatments were either by transurethral fulguration or by radiotherapy.

A Riches cystoscope and crocodile forceps (*Fig.* 269) were used. Full inspection of the tumour was carried out; its general physical characteristics and adjacent nodules or other abnormality of the bladder mucosa were noted. The examining telescope was then replaced by the operating slide, and the crocodile biopsy forceps were passed through the central channel until the jaws of the forceps could be seen through the telescope (*Fig.* 270). The Albarran lever was manipulated and the jaws of the forceps were approximated to the tumour. (The forceps were always tested before use by closing the jaws and pulling on a piece of gauze: the jaws should not slip off the gauze.) When the tumour was situated on the bladder base or low down on the lateral walls, the jaws of the forceps could easily be manipulated into or onto the tumour and a portion of tumour tissue grasped and withdrawn. Opening the withdrawn forceps and shaking them in a specimen jar containing fixative allowed pieces of tumour tissue to fall off and be easily seen. It is advisable to take two or three bites; the whole procedure seldom takes longer than ten minutes. Undue hæmorrhage or other complications have not been observed.

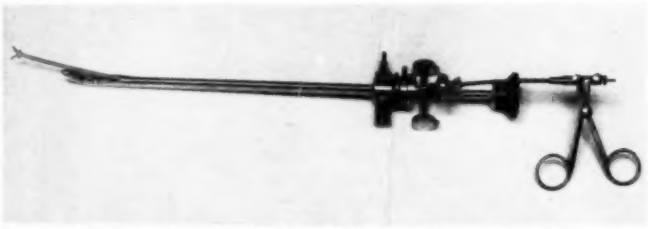


FIG. 270.—The cystoscope showing the crocodile forceps in position.

When the tumour is less readily accessible, the opened jaws of the forceps are manipulated as near as possible to the tumour, and the bladder slowly emptied; the tumour then usually comes down into the open jaws. Difficulty is liable to occur when the growth is situated at the vault of the bladder. Failure to obtain an adequate biopsy occurred in only one case.

When multiple tumours exist, biopsy specimens should be obtained from as many sites as possible.

Table I.—HISTOLOGY IN 20 CASES IN WHICH COMPARISON WAS POSSIBLE BETWEEN THE MICROSCOPIC APPEARANCE OF THE BIOPSY AND THE BULK OF WHOLE TUMOUR (*Cases* 1–18 showed Exact Correlation)

CASE	HISTOLOGY OF BIOPSY	BULK OF TUMOUR
1	Highly proliferative papillary carcinoma	Same
2	Malignant papillary tumour	Same
3	Squamous carcinoma	Same
4	Anaplastic carcinoma of great cellular pleomorphism	Same
5	Fairly well differentiated villous carcinoma	Same
6	Poorly differentiated transitional cell carcinoma	Same
7	Malignant villous tumour	Same
8	Transitional cell carcinoma	Same
9	Moderately well differentiated papillary carcinoma	Same
10	Transitional cell carcinoma	Same
11	Degenerating anaplastic carcinoma	Same
12	Anaplastic pleomorphic carcinoma	Same
13	Well differentiated transitional cell carcinoma	Same
14	Pleomorphic edge of a malignant tumour	Same
15	Actively growing benign papilloma	Same
16	Anaplastic transitional cell carcinoma	Same
17	Villous papilloma	Same
18	Poorly differentiated transitional cell carcinoma	Same
19	Transitional cell papillary carcinoma with cellular atypism and numerous mitoses	Carcinoma of bladder not showing any papillary tendency but with slight squamous differentiation
20	Necrotic tissue: no malignant cells found	Poorly differentiated transitional cell carcinoma

RESULTS

Of 32 cases in which it was not possible to examine the bulk or whole of the tumour, 21 were diagnosed after biopsy as transitional cell papillomata, 1 a subepithelial fibroma, and 10 malignant.

In the 22 cases where the primary histology was benign, the subsequent clinical course of the patients cast little or no doubt on the diagnoses.

In the 10 patients in whom the histology of the biopsy was malignant, 2 refused further operation, 6 were treated by the linear accelerator, and 2 are awaiting further treatment.

In 20 cases it was possible, either because the patients underwent radical surgery, or died and were examined at post mortem, to compare the histology of the biopsy with the bulk or whole of the tumour (*Table I*); in 18 of these the histology was identical.

In 2 cases in which there was a discrepancy in histological findings, necrotic debris was found in the biopsy specimen in one when, in fact, the growth proved to be an anaplastic carcinoma. A transitional cell papillary carcinoma was present in the biopsy of the other when, in fact, the tumour was a solid carcinoma with slight squamous differentiation (*Fig.* 271).

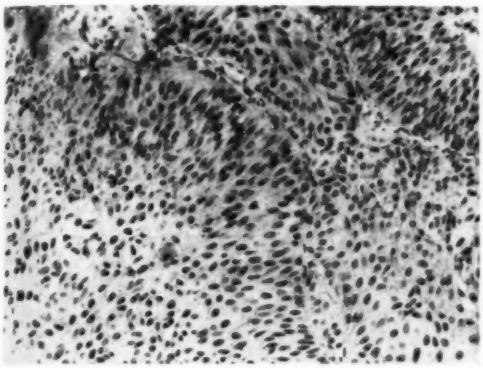
DISCUSSION

This report strongly suggests that biopsy in cases of bladder tumour affords an accurate preoperative histological picture. It is not felt that the results in the present series are due to chance and it

is anticipated that a larger series will not alter the statistical variation.

When it was possible to make histological comparison, correlation was found in 18 out of 20 cases (90 per cent). Although it was not possible to make the comparison in 22 other patients with benign tumours, there is every reason to believe, as a result of subsequent clinical and cystoscopic follow-up, that the histology of the biopsies was representative of the whole or bulk of the tumours.

The technique has proved to be simple and safe; it is recommended before any form of definitive treatment is undertaken, and should not be reserved only for the doubtful case of bladder carcinoma.



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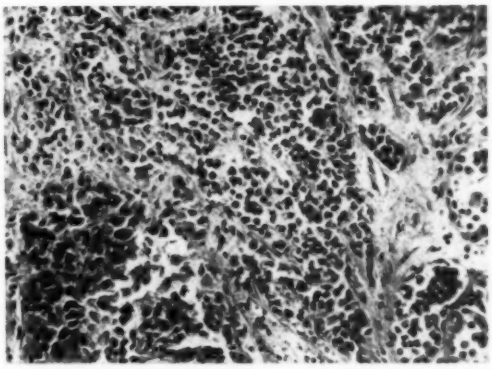

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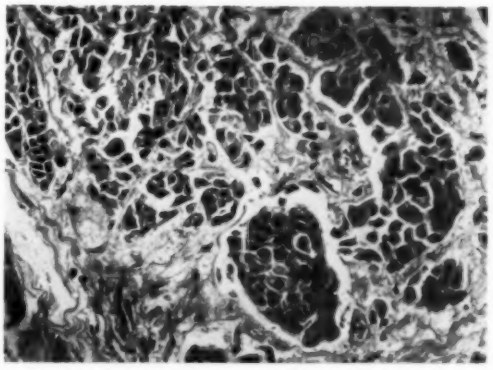

C

FIG. 271.—A, Photomicrograph of the histological biopsy specimen of *Case* 19, showing a transitional cell papillary carcinoma. B, C, Photomicrographs of parts of the excised tumour (*Case* 19), showing a solid carcinoma (B) with slight squamous differentiation (C). These appearances disagree with the appearance of the biopsy specimen shown in (A).

SUMMARY

1. A simple and safe method of transurethral biopsy for bladder tumours is described.

2. The degree of histological correlation between the transurethral biopsy and the whole or bulk of the bladder was studied. Excellent correlation was found.

3. Absence of subjacent bladder muscle in the biopsy did not invalidate the histological diagnosis.

Acknowledgements.—The Department of Pathology has been responsible for the histological findings and the author gratefully acknowledges this contribution. The illustrations are by the Department of Medical Illustration at the Postgraduate Medical School, London.

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INGUINAL HERNIA

A THREE-YEAR REVIEW OF ONE THOUSAND CASES

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INTRODUCTION

Surgeons have always been troubled by the problem of the best method of repairing an inguinal hernia. Medical literature, from the *De Medicina* of Celsus in A.D. 30 to the latest medical journals, contains frequent references to the problem. Many famous surgeons—Guy de Chauliac, Ambroise Paré, Percival Potts, Astley Cooper—have written treatises about it, and there is not a surgeon to-day who would claim that the final word is yet written on the subject.

Up to the sixteenth century, the prevailing method of repair involved the sacrifice of the testicle. Paré's influence led to the abandonment of castration and the seeking of more conservative surgical methods. It was, however, the work of Bassini in Italy, published in 1889, and Halsted in the United States, in 1889 (Catterina, 1934; Watson, 1938), which formed the basis of modern techniques. Bassini's advocacy of open dissection of the inguinal canal, division of the hernial sac within the internal ring, and strengthening of the posterior wall of the canal, was in marked contrast with surgical opinion prior to 1883, which had, in the main, favoured a division of the sac at the external ring. His principles still stand as the basis of the majority of operations for inguinal hernia carried out at the present time. In more recent times, techniques have become extremely variable, ranging from simple excision of the sac with or without a narrowing of the internal ring, to the strengthening of the posterior wall by insertions of foreign material such as polyvinyl sponge or nylon tricot. This profusion of methods has been the result of three causes.

1. *The publication of unsatisfactory results of previously accepted methods.* Page's (1934) studies of the results of repair in London policemen were particularly effective in causing dissatisfaction with the Bassini operation. Bassini had reported a recurrence rate of only 3·3 per cent—7 cases in 216 operations. In 1934, Page's investigations revealed a recurrence rate of over 20 per cent for oblique herniæ in a survey of 295 consecutive cases. In a later series (Page, 1943), examined between 3 and 6 years after operation, 12 per cent of a smaller series of oblique herniæ had recurred. At the Royal Society of Medicine in November, 1943, Edwards estimated that the recurrence rate after an inguinal hernia operation was at least 12 per cent, and he stated: "Recurrence is actually and relatively more common after the Bassini operation than any other, and for this reason I think the operation should be abandoned".

2. *The study of the anatomy of the inguinal canal by anatomists, surgeons, and even radiologists with surgical assistance.* These studies have yielded a very exact knowledge of the mechanism of the closure of the canal during straining, with consequent efforts by surgeons either to avoid damaging the mechanism or to repair it when damaged. Lytle's paper in the British Journal of Surgery (1945) added considerable strength to the views of Ogilvie (1937) and Edwards (1943 a, b) with respect to the conservation of the normal musculature directing the repair to the internal ring and fascia transversalis. Bassini himself had, of course, stressed the importance of the transversalis fascia, and particularly of its repair just medial to the cord at the internal ring (Catterina, 1934).

3. *The production of non-absorbable materials which are chemically inert when left within the body.* It was even claimed that the great disadvantage of silk, viz., that if infection supervened it would persist until the silk had been removed or discharged, did not apply to nylon which, it was said, would not hinder the overcoming of infection.

In fact, many surgeons have followed Hunter's dictum: "Why think? Why not try the experiment?" Many more surgeons, however, have chosen rather to follow Paré's advice: "A remedy thoroughly tested is better than one recently invented", and probably the commonest method of repairing an inguinal hernia to-day is still that of Eduardo Bassini. The difficulty lies, of course, in the words "thoroughly tested", as the results of inguinal hernia repair are very difficult to assess, particularly in a manner allowing comparison between the results of differing techniques. There is, however, no alternative to facing the difficulty. It is only by a comparison of results that the problem can be solved. A great deal depends on what is meant by 'recurrence rate'.

STATISTICAL DIFFICULTIES

The difficulty of compiling accurate and comparable statistics relating to the results of inguinal hernia repair is due to the large number of varying factors. These may be grouped as follows:—

1. Those relative to the patient:—

a. The type of hernia—oblique, direct, recurrent.

b. The degree of damage to the inguinal canal (fascia and muscles), often proportional to the duration of the hernia.

c. The condition of the patient's musculature, often varying with his age.

d. The degree of obesity.

2. Those relative to the surgeon:—

a. The method of repair.

b. The degree of surgical skill.

3. Those affecting the strain to which the repair is subjected:—

a. The time of 'getting-up' and of return to work.

b. The nature of the patient's work.

c. Intercurrent disease, particularly if associated with a chronic cough.

d. The period of time between the repair and its review.

4. The examiner's standards of the soundness of a repair.

By studying large numbers of patients, subdividing according to the type of hernia, method of repair, degree of exposure to strain after operation, etc., many of the above variables may be eliminated. In most reviews, however, three of the above factors are

particularly troublesome, preventing the production of comparable statistics; these are the individual surgeon's skill, the period of time between the repair and its review, and the examiner's standards.

In 1951, at the suggestion of Professor Charles Wells, a scheme was started whereby in four General Hospitals of the United Liverpool Hospitals—the Royal Infirmary, the David Lewis Northern Hospital, the Royal Southern Hospital, and the Liverpool Stanley Hospital—the repair of every inguinal hernia in a male subject of 16 years or over was registered. Each patient on the register was to be examined at the end of one year, and again at the end of three years. The scheme was later modified to exclude:—

1. Private patients.
2. Patients living at far distances (over 25 miles) from Liverpool.

Three further groups of patients are necessarily eliminated:—

3. Those who have died before review.
4. Those who have developed a chronic illness preventing their attendance for examination.
5. Those untraceable by the postal authorities or Local Executive Council.

The scheme has worked and is working well, and the present paper is based on the first thousand 3-year reviews. In it, the time of review is uniform and one examiner has carried out all the reviews. The third difficulty of 'surgical skill' is eliminated to a large extent by the large number of surgeons concerned and the fact that two-thirds of the operations are carried out by registrars who move from one surgical team and hospital to another at yearly intervals. As a registrar usually adopts the technique of repair favoured by his team, the result is that over the years most of the techniques are tried out by most of the registrars.

Criteria of Recurrence.—Soon after the start of the scheme certain difficulties became apparent. The most important of these was the definition of a standard of recurrence. Harold Edwards (1943 a) has written: "One of the most important variants [affecting the statistics] is in the criteria of recurrence adopted—an important point. A small though definite bulge after operation may be discounted by some—and this will reduce the recurrence figure by 50 per cent, according to Grace and Johnson (1937)." In a series of cases examined by the present writer, several of the men examined ten to thirteen years after the repair had their attention drawn to a small local bulge. Almost all of them asserted that this appeared soon after their operation, and had not deteriorated. In contrast, a young man had an oblique inguinal hernia repaired in 1935, he was well satisfied with the repair, and he was considerably surprised when on joining the Services in 1941 he was told that he had a recurrence, and was provided with a truss. He did in fact, however, wear this for only a short time. He carried on in civilian life after the end of the war, quite confident of the soundness of his repair, until he finally noticed a recurrence himself in 1951, which was repaired. Here, apparently, was a localized bulge developing into a true hernial sac after ten years.

The presence of a recurrent sac is by no means always easily decided. When the external oblique has been sutured behind the cord, so that the internal and external rings are approximated, there is often a vascular thrill in the cord on coughing, which simulates a small sac very closely, especially if there is a varicocele. After this type of repair, too, there is often a certain degree of protrusion at the site of emergence of the cord, which in no way indicates a weakness. Furthermore, deterioration of the inguinal musculature with the passage of years may lead to a small or even large diffuse bulge, not truly a recurrence.

In the present series, at the 1-year examination a 'small but definite bulge' was noted in 81 cases, quite apart, of course, from the definite recurrent cases. At the 3-year examination 73 of these had remained unchanged, 6 had deteriorated so as to be classed as definite recurrences, while 2 had actually improved. In the same period, 6 repairs, quite sound at the 1-year examination, were recurrent 2 years later. Accordingly, a 'small but definite bulge' has not been classified as a definite recurrence unless later examination (usually after 6 months) shows deterioration. Furthermore, there may occasionally be found after operation at the pubic end of the canal a small incompletely reducible swelling, enlarging on straining, which is quite symptomless and, in fact, usually unknown to the patient. Often progressing to a complete recurrence, many of these remain unchanged for years, if not indefinitely, and are very similar to herniæ of the linea alba. Like so many epigastric herniæ, they do not require any treatment. They do not represent, therefore, a failure of the original operation, which is designed to rid the patient of an inconvenient and often dangerous disability, and has done so even if followed by a 'recurrence' of this 'linea alba' type. In the present series, apart from 57 definite recurrences, there were 5 of the 'linea alba' type.

Occasionally, a femoral hernia follows closely on the repair of an inguinal hernia (twice in the present series). These have not been classed as recurrences.

Summing up, therefore, a recurrence is defined as a weakness of the operation area, necessitating a further operation or the provision of a truss. Defined in this way as the obvious failure of the operation, a uniform standard of recurrence is much more likely to be obtained than if the slighter degrees of weakness—the importance of which is controversial—are included as recurrences. No doubt, if such a standard were generally accepted, Page's figures of 20 per cent and even Edwards's 12 per cent would be considerably lower. They would, however, be also more practical and more valuable in that they would be more comparable. Any general practitioner would throw scorn on the view that 1 in 5 inguinal herniæ recur after operative repair. Patients, too, would not come so readily for operation if the experience of their fellows did not indicate better results than these.

One further advantage of this restricted definition of a recurrence is that as it represents the failure rate it might be possible to obtain reliable statistics by a postal questionnaire, which would probably yield a follow-up of over 90 per cent at 3 or even 6 years.

Time of Recurrence.—The time of the examination of a wound for a recurrence is of the greatest importance. In the present series, 45 repairs were recurrent at the end of the first year. Twelve

more of those previously sound were recurrent at the end of 3 years.

Under the present scheme, and through the records of a pilot scheme in a large regional hospital,* and personal records, there are immediately available

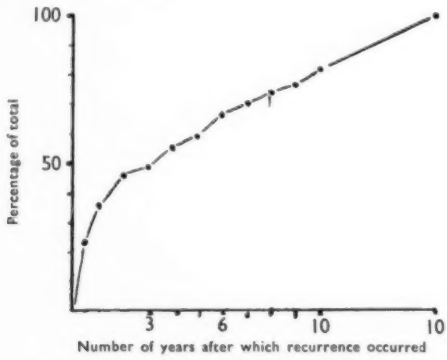

FIG. 272.—Percentage of recurrences occurring in each year after operation.

the histories of 230 recurrent inguinal herniæ subjected to further operation (*Table I*); these have been arranged in the form of a graph showing the percentage occurring in each year after operation (*Fig.* 272).

There can be no doubt, therefore, that the recurrence rate must be qualified by the time of

Table I.—TIME OF ONSET OF RECURRENCE (230 Cases)

Within 6 mth.	56
Between 6 and 12 mth.	29
2nd yr.	22
3rd yr.	7
4th yr.	11
5th yr.	12
6th yr.	13
7th yr.	11
8th yr.	8
9th yr.	7
10th yr.	13
After 10 yr.	41

examination after operation. Under the present scheme, that time has been kept uniform at 3 years as a time when a fair percentage of patients can be persuaded to attend for examination (82 per cent so far),† and yet sufficient time has passed to allow a reasonable, though by no means complete, testing of the success of the operation.

* In 1951 and 1952 a series of inguinal hernia repairs effected at a large regional hospital (Whiston Hospital) between 1939 and 1950 were examined, at intervals ranging between eighteen months and 13 years after operation; of 859 cases, 611 were examined. Unfortunately, the varying period of follow-up prevented a satisfactory comparison of the results achieved by varying methods of repair, and the results remain unpublished. Some use has, however, been made of the findings of that scheme in this paper.

† A high follow-up rate is very difficult to achieve when the subjects are working men without any residual disability. It is particularly difficult in Liverpool, where a large proportion of the patients are seamen; about half the missing 18 per cent are of this occupation.

Type of Hernia.—Classification of herniæ into oblique and direct was occasionally difficult, as in many cases both elements were present. If a definite oblique sac was present, however, it was classified under oblique unless the sac was of the pantaloon variety, when the hernia was recorded as direct.

FINDINGS

The present paper is based on the 3-year review of 1000 inguinal herniæ repairs, of which in 182 cases the patients failed to attend for examination, although information with regard to the soundness of the repair has been obtained either from the patient or his doctor in 84 of these cases, the report in every case being that the repair was sound. Unless stated to the contrary, recurrence rates are based on the 818 cases seen by the author or subjected to a further repair. Many of the 182 non-attenders did, however, attend for examination at one year, and use has been made of this material in presenting the complication or morbidity rates which are based on 976 cases. Finally, as stated at the beginning of this report, the 1000 cases have been selected from a larger number, 1122 in all, and the mortality has been calculated on this figure.

Type of Hernia.—It has been noted already that any statement of a recurrence rate must be qualified by a definition of 'recurrence', and by the period of time between the repair and its review. Of no less importance is the type of hernia repaired. For this purpose, inguinal herniæ should be divided into three groups: (1) Primary oblique ; (2) Primary direct ; (3) Recurrent or secondary. A series with a large number of the direct, or particularly the recurrent type, will have a higher recurrence rate than one containing mainly primary oblique herniæ. In the present series there were 57 recurrent cases in 818 repairs, i.e., an overall 3-year recurrence rate of nearly 7 per cent. These were distributed between the types of hernia as shown in *Table II*.

Table II.—OVERALL 3-YEAR RECURRENCE RATE IN 57 CASES OF HERNIA REPAIR

	Primary Oblique Hernia	*Primary Direct Hernia*	*Recurrent Hernia*
Sound at 3 years	532	184	42
Recurrent	29	16	12
3-year recurrence rate	5 per cent	8 per cent	22 per cent

Three cases were excluded from this table because the operation notes did not establish clearly whether the hernia was of the primary oblique or direct type.

Primary Oblique Inguinal Hernia (561 Herniæ).—Of the 29 recurrent cases, 19 were subjected to further operation and were found to have oblique sacs in 16 cases and direct in 2 cases (in the remaining case there was no note of the type of sac, but clinically it appeared to be direct). The remainder of patients were provided with a truss, but clinically the recurrence appeared to be of the oblique type in 6 cases and direct in 4. Three-quarters of these cases, therefore, represent a return of the previous oblique sac, but one-quarter represents the damage done by the operation to the previously intact posterior wall of the canal. In addition, there were 4 cases of 'linea alba' herniæ,

all quite symptomless: 1 of 4-years' duration now, 2 of 2½ years, 1 of 6 months only.

In the hope of identifying the factors involved in the failure of the operative repair in these particular cases, details of the status of the surgeon, age, physique, and degree of obesity of the patient, discomfort or disability, he refused operation. Two and a half years later, there has been no deterioration of his condition.

As with oblique inguinal herniæ, various possible causative factors in recurrence have been noted and arranged in *Tables III–VIII.*

Table III.—Surgical Skill as a Factor in Recurrence of Hernia

Status of Surgeon	Type of Hernia						Total	
	Primary Oblique		Primary Direct		Recurrent			
	Total	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*
House surgeon	13	1	9	3	0	0	22	4
Registrar	370	21	129	10	22	3	521	34
Visiting staff	178	7	60	3	32	9	270	19

duration of the hernia before operation, type of work done after operation, and time of getting up after operation have all been drawn up in *Tables III–VIII.*

Secondary or Recurrent Inguinal Hernia (54 Herniæ).—Four of the 12 secondary herniæ which had again recurred were explored, with the

Table IV.– Age of Patient as a Factor in Recurrence of Hernia

Age of Patient (years)	Type of Hernia						Total	
	Primary Oblique		Primary Direct		Recurrent			
	Total	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*
16–30	113	5	7	0	9	1	129	6
31–45	161	7 (1)*	66	2	17	5	244	14
46–60	213	12 (4)*	99	11 (5)†	21	3	333	26
61 +	74	5 (2)*	26	3	7	3	107	11

* Direct hernia. † Oblique hernia.

The other very important factors of technique and sepsis are discussed later.

Primary Direct Inguinal Hernia (200 Herniæ).—Of the 16 recurrent cases, only 4 were subjected to a further operation, a direct sac being found in each case. The remaining 12 were provided with a truss but—surprisingly—5 of these appeared clinically to have recurrent *oblique* sacs. In 2 of these cases there had been a small associated oblique sac at the primary operation—1 being of the pantaloon variety—but the other 3 had been completely direct. It may be that repair of the posterior wall sometimes damages the mechanism controlling the internal ring.

In addition, there was 1 hernia of the 'linea alba' type; when first seen, this patient was advised to have a further repair. Having been previously unaware of the small swelling, and having no finding of an oblique sac in only 1 case. The remaining 8 patients, provided with a truss, *appeared* to have oblique sacs in 2 cases and direct in 6. It is, however, very difficult to determine clinically the site of origin of a recurrent sac after *two* previous operations. Here, again, the various possible factors associated with the recurrence have been noted in *Tables III–VIII.*

Table V.—Physique and Obesity as a Factor in Recurrence of Hernia

Physique and Obesity	Type of Hernia						Total	
	Primary Oblique		Primary Direct		Recurrent			
	Total	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*
Good	110	4	19	0	7	0	136	4
Moderate	352	19	136	13	39	8	525	40
Poor	89	6	42	2	7	2	138	10
Obese	68	6	29	2	3	1	100	9
Non-obese	492	23	171	14	51	11	714	48

Possible Factors associated with Recurrence.—

1. *Status of Surgeon.*—The degree of success of repairing the three types of inguinal hernia achieved by different degrees of surgical skill are set out in *Table III.* Allowing for the fact that, in general, the more difficult cases are done by the visiting surgeon, their results are strictly comparable with those of the registrars.

2. *Age of Patient.*—It is sometimes stated that patients in the middle-aged groups around 45 years are the ones showing a higher percentage of recurrence because they are more exposed to physical stress after operation; this is not borne out by *Table IV*, which shows a steady deterioration of the results with increasing age. It also illustrates the increasing predominance in the higher age-groups of the direct recurrence after a repair of a primary oblique hernia.

3. *Physique and Obesity.*—Unfortunately, degrees of physique are difficult to estimate, and the standards used here are by no means exact, a similar criticism applying to a definition of obesity. Nevertheless, *Table V* confirms what would be expected—a worsening of the results with a worsening physique, and better results in the non-obese than in the obese.

5. *Work after Operation.*—*Table VII* has been drawn up to show the effects of work after operation. The division into heavy and light-to-moderate work depends on the patient's estimate, and is therefore only approximate. Even so, the figures are surprising. They are confirmed, however, by the findings at Whiston Hospital (*see* footnote, p. 236) where the recurrence rate amongst the heavy manual workers was no higher than amongst the remainder.

6. *Time of Getting Up.*—*Table VIII* relates the results to the period of *absolute* confinement to bed after operation. There is no striking difference except in those cases where the period is over 10 days, and many of these patients were probably confined to bed because of age or sepsis, or pulmonary infection, the poor results in this group being due to the complications rather than the confinement to bed. The figures do illustrate, however, the rapid mobilization of the patients nowadays—a very far cry from Bassini's enclosure in plaster-of-Paris and confinement to bed for six weeks (Watson, 1932).

Table VI.—Duration of Hernia as a Factor in Recurrence Rate

Duration of Hernia (months)	Type of Hernia						Total	
	Primary Oblique		Primary Direct		Recurrent			
	Total	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*
Under 3	242	11	88	7	14	1	344	19
3–12	135	4	40	1	21	6	196	11
Over 12	181	13	72	8	19	4	272	25

Table VII.—Work after Operation as a Factor in Recurrence of Hernia

Work done after Operation	Type of Hernia						Total	
	Primary Oblique		Primary Direct		Recurrent			
	Total	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*
Heavy	216	11	37	1	14	2	267	14
Light to moderate physical work	207	12	88	6	28	7	323	25
Sedentary, supervisory, or no work	138	6	73	9	12	3	223	18

Table VIII.—Time of Getting Up after Operation as Factor in Recurrence of Hernia

Time of Getting Up (days)	Type of Hernia						Total	
	Primary Oblique		Primary Direct		Recurrent			
	Total	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*
1–5	289	9	112	10	20	2	421	21
6–10	124	8	47	2	16	2	187	12
10 +	142	9	40	3	16	6	198	18

4. *Duration of the Hernia.*—*Table VI* shows no obvious worsening of the results until the history has lasted for over a year. This obviously only applies in a general way. In many cases it is self-evident that increasing size with the passage of time indicates increasing damage to the inguinal musculature, with a greater prospect of a recurrence. *Table VI* does illustrate, however, the time lost by the patient before seeking advice. The time-loss of the surgical waiting list in the United Liverpool Hospitals rarely exceeds a month.

Technique of Repair.—There can be no other operation so commonly performed as the repair of an inguinal hernia, nor one in which there is so little agreement about the details of the technique. Not merely the larger steps of conservative measures versus more radical procedures, or the advantages and

disadvantages of catgut, thread, silk, nylon—monofilament and braided—mersaline, fascia, and wire as suture materials, but even the smaller details of a relaxation incision, removal or preservation of the cremaster muscle, division of the cremasteric vessels, or preservation without even disturbance of the ilio-hypogastric nerve, are stressed by some surgeons and ligament behind the cord by a continuous suture formed from a strip of external oblique, left attached at the symphysis pubis. If the strip is long enough, it is often used to repair the central part of the divided external oblique immediately anterior to the cord. It is secured with fine sutures of non-absorbable material, usually nylon.

Table IX.—Comparison of Results of Different Techniques of Hernia Repair

No.	Type of Repair	Type of Hernia					
		Primary Oblique		Primary Direct		Recurrent	
		Total	*Recurrence*	*Total*	*Recurrence*	*Total*	*Recurrence*
1	McArthur-Morrison	168	11 (6·5 per cent)	54	5 (9 per cent)	7	1
2	Bassini with nylon	91	4 (4·5 per cent)	39	2 (5 per cent)	11	2
3	Bassini with mersaline	25	0	—	—	—	—
4	Bassini with catgut	47	2 (4 per cent)	14	3 (21 per cent)	2	1
5	Bassini W.A.* III, nylon	56	2 (4 per cent)	45	4 (9 per cent)	6	0
6	Bassini W.A. III, mersaline	20	1 (5 per cent)	12	0	1	0
7	Bassini W.A. III, catgut	2	2	1	0	—	—
8	W.A. III, catgut	15	0	5	0	2	1
9	W.A. III, nylon	—	—	—	—	2	0
10	W.A. II, catgut	36	0	9	0	3	0
11	W.A. II, nylon	5	0	—	—	—	—
12	W.A. II, mersaline	1	0	—	—	—	—
13	Bassini W.A. II, catgut	8	1	4	0	—	—
14	Bassini W.A. II, nylon	—	—	1	0	—	—
15	Closure of canal	30	0	1	0	6	2
16	Cooper's	2	0	3	2	—	—
17	Gallie	4	2	3	0	2	0
18	Nylon tricot	27	2 (7·5 per cent)	7	0	4	0
19	Excision of sac	16	0	—	—	—	—
20	Excision of sac and closure of internal ring	12	1	—	—	—	—
21	Fascia transversalis	4	1	1	0	—	—

* W.A.—Wyllys Andrews

dismissed as unimportant by others. The importance of many of the small details cannot be proved or disproved in a series such as this. A parallel individual series of cases is, however, being studied where note is made of many of these points. The larger steps of technique have been noted, and in the following paragraphs their relative values are compared—as far as is possible—with reference to primary oblique and direct herniæ. Recurrent herniæ are so individual in their nature that it is scarcely possible to compare the results of the application to them of one technique with that of another. However, all the results are shown in *Table IX*.

McArthur-Morrison (*No.* 1).—This has been the technique most commonly practised, consisting in the apposition of the conjoint tendon and inguinal

The resulting 11 recurrences in 168 primary oblique herniæ and 5 recurrences in 54 direct herniæ form a standard for comparison with other techniques. A study of the recurrences, many of which have had a further operation, has shown that almost invariably a firm union of the conjoint tendon and inguinal ligament has been secured. Unfortunately, however, the region of the internal ring has not been well controlled in some cases, allowing the formation of a further oblique sac, whilst in others the thick suture appeared to have split the conjoint tendon at its inner part, with the production of a pubic recurrence.

Bassini (*Nos.* 2–4).—In this report, Bassini's name has been applied quite incorrectly, but very conveniently, to the simple apposition of the conjoint tendon and the inguinal ligament behind the cord

throughout the length of the canal; the McArthur technique would be a 'Bassini' with an external oblique strip. The Bassini technique is also used very frequently, often with the addition of some minor modification such as the narrowing of the internal ring or a Tanner relaxation incision. The suture material is nylon, mersaline, or catgut, and when unabsorbable sutures are used the figures of 4 recurrences in 116 oblique cases and 2 in 39 direct cases compare favourably with the McArthur operation.

Wyllys Andrews III (*Nos.* 5–7).—This has been used incorrectly, but very conveniently, for the simple suture or overlapping of external oblique behind the cord, i.e., the subcutaneous transposition of the cord, a procedure first described by Halsted (Watson, 1938). In most cases the Bassini technique has preceded the W.A. III as in Halsted's original operation, actually abandoned by him in 1903. Here, again, when unabsorbable sutures have been used, the figures of 3 recurrences in 76 oblique herniæ and 4 in 57 direct compare favourably with the McArthur technique. They are, however, no better than the Bassini figures, and it must be doubted whether the W.A. III part of the technique gives any greater security. In a few cases (Nos. 8–9) the W.A. III technique has been used alone, with excellent results, but the numbers are too few for comparison.

Wyllys Andrews II (*Nos.* 10–14).—This technique is carried out by only one surgical team, and consists in bringing down the upper flap of external oblique to the inguinal ligament behind the cord, and bringing up the lower flap in front of the cord, so that the cord lies between the two flaps of external oblique. Behind this, the posterior wall is strengthened by the suture of the fascia transversalis to the inguinal ligament; many of the registrars replace this latter step by a Bassini technique. The overall figures of only 1 recurrence in 50 oblique cases and none in 14 direct are startling, despite the small number. It must be admitted, however, that the greater number of these repairs were carried out by one senior surgeon, and it is at least probable that the factor of surgical skill plays a great part in the good results of this technique. In most cases the suture material was catgut, in contrast to the previous methods.

Closure of the Canal (*No.* 15).—In 7 cases the canal was closed because the testicle was undescended; in 6 of these cases the testicle was removed as it could not be brought into the scrotum; in the seventh case the testicle was not seen, and was presumably abdominal. In 30 cases the canal was closed completely after either orchidectomy or division of the spermatic cord, usually because the patient was old or because a recurrence was thought to be likely. Nineteen patients were over 60 years of age and 27 over 45 years. The 2 cases which did recur were in secondary herniæ in men under 45 years of age. The canal was closed with nylon in 24 cases (2 of these recurred), with catgut in 7 cases, with an external oblique strip in 3 cases, and with unspecified suture material in 3 cases. In the whole series the cord was divided in 11 cases, and on two occasions an orchidectomy was required because of painful swelling of the testicle. In 3 cases, however, the testicle appeared to be normal 3 years after operation. One patient developed a small hydrocele and 2 further testicles atrophied. The remaining 3 testicles gave no trouble, but no note has been made as to whether atrophy occurred.

It is worth noting that of the 16 cases of inguinal herniæ associated with an undescended testicle, all remained sound after 3 years. Seven were dealt with as above, the remaining 9 being subjected to orchidopexy, with success in only 4. Three testicles atrophied, 1 retracted and needed an orchidectomy because of pain. Twelve of these cases were in the 16–30 age-group.

Table X.—Recurrence Rate of Hernia with Other Techniques

	Primary Oblique Hernia		Primary Direct Hernia	
	Total	Recurrence	Total	Recurrence
Tanner relaxation incision	52	1	37	1
Narrowing of internal ring	83	3	6	0

Considering that closure of the canal is reserved in the main for those cases which are thought to be particularly likely to recur, the absence of a single recurrent case in 30 oblique and 1 direct inguinal hernia is very satisfactory.

Nylon Tricot (*No.* 18).—In this repair, after a Bassini procedure, a piece of nylon tricot is sutured over the posterior wall—to the inguinal ligament below, the rectus sheath medially, the conjoint tendon and internal oblique above, with a sleeve around the cord laterally as it emerges through the internal ring. This method also is used by only one surgical firm, most of the repairs being effected by this method; it is not reserved for the more difficult cases. The results of 2 recurrences in 27 oblique herniæ are somewhat disappointing, therefore, although partly compensated by the absence of recurrence in 7 direct herniæ; both recurrences were—unexpectedly—of the direct type.

Conservative Methods (*Nos.* 19, 20).—In 28 oblique inguinal herniæ a simple excision of the sac was effected, combined in 12 cases with a narrowing of the internal ring. There was 1 recurrence in the latter group, a disappointing result, considering that these cases were all young men with satisfactory musculature.

Finally, there are the very few herniæ repaired by Gallie's method (17), by the approximation of the conjoint tendon to Cooper's ligament (16), and by the strengthening of fascia transversalis alone without disturbance of the conjoint tendon (21). Their numbers are too few for comparison, but they are inserted to illustrate the variety of methods used.

Two other points of technique are of importance: the Tanner relaxation incision and the narrowing of the internal ring.

Tanner Relaxation Incision.—A relaxation incision was presumably made mainly in those cases in which the conjoint tendon was high and in which a Bassini procedure would be effected only with some tension—a factor not conducive to a sound repair. This being so, the results of only 1 recurrence in 52 oblique cases

and 1 in 37 direct (*Table X*) are indicative of the soundness of the procedure. It was carried out mainly in those cases repaired via the 'Bassini with nylon' method.

Narrowing of Internal Ring.—A deliberate narrowing of the fascial margins of the internal ring is effected almost as a routine procedure by several surgeons in combination with a radical repair; in all, in 83 oblique herniæ and 6 direct ones (*Table X*). The 3 recurrences were all oblique, which is disappointing, and, of course, these results are only slightly better than the radical repair alone.

Table XI.—Relation of Sinus Formation to Suture Material used

Type of Repair	Number of Cases	Duration of Sinuses	Number of Further Operations
McArthur, secured with nylon	3	3 mth., 6 mth., 15 mth.	2
Bassini with nylon	3	2 mth., 3 yr., 3½ yr.	4
Bassini with mersaline	1	2½ yr.	2
Bassini W.A. III with nylon	5	6 mth. (2), 12 mth., 18 mth. (2)	4
W.A. II with catgut	1	4 mth.	0
Closure of canal with nylon	4	3 mth., 9 mth., 2 yr., 5 yr.	6
Cooper's with nylon	1	12 mth.	1
Nylon tricot	3	6 mth., 8 mth., 12 mth	4
Fascia transversalis with nylon	1	4 mth.	Nylon discharged spontaneously

Morbidity.—Infection and its aftermath—the chronic sinus—are the most important complications of an inguinal hernia repair. Pain in the wound or in the testicle, hydrocele, testicular atrophy, or impotence are other complications, but the commonest complication of all is a hæmatoma either in the subcutaneous tissues or in the spermatic cord. Subcutaneous collections of blood or serum are important only in that they are liable to become infected; the spermatic-cord collections are a nuisance in that they may be very large yet difficult to aspirate. They are, however, absorbed remarkably completely within a few months and are, therefore, better left alone.

Chronic Sinus.—Out of the 976 cases followed up for at least one year, 54 are known to have become infected after operation. An infection rate of over 5 per cent is surprising for 'clean surgery', even though the operation area is a difficult one to sterilize, and—perhaps more important—a difficult one to keep sterile after operation. Several patients had an appendicectomy via the sac, one had a Meckel's diverticulum excised, in another the cæcum was accidentally laid open (this repair was effected with nylon!). None was followed by infection! One hundred and fifty years ago, infection had led Sir Astley Cooper to teach that an inguinal hernia should not be dealt with by surgery unless it were strangulated, and even then he merely divided the constriction and reduced or excised the hernial contents, not attempting to repair the defect in the inguinal canal or even to excise the sac, but merely suturing the skin and providing a truss afterwards. Those days have passed, however, and when Bassini reported his results in 1889 his infection rate was only 5 per cent—and that without sterile gloves and gowns, but just a rubber apron for the surgeon and a few clean towels for the operation area! (Catterina, 1934). Admittedly, 20 of the 54 infected cases may be dismissed as stitch abscesses or infected subcutaneous hæmatomata—an uncomfortable but quite minor disturbance of the post-operation period. Of the remainder no less than 22 yielded a sinus which took over two months to heal, and, in fact, 11 of these took a year or more to heal; and in the process of healing no less than 23 further operations for the removal of non-absorbable sutures were required. Finally, out of the 54 infected cases, 10 recurred—surely proof that sepsis is an important factor leading to recurrence.

From *Table XI* it can be seen that in all except 5 cases nylon was the principal suture material, whilst in the 3 McArthur repairs the external oblique strip had been secured with nylon, and in 2 of them healing did not take place until a nylon knot had been removed. Thus in all but one case, non-absorbable sutures of a foreign material were almost certainly responsible for the sinus, and in the solitary case associated with catgut, healing was comparatively rapid and was secured without surgical intervention. This represents a severe indictment of nylon and mersaline as suture materials.

Strangulation.—In the whole series of 1122 cases there were only 20 herniæ which were strangulated at operation, although at least 5 more had been strangulated on admission to hospital, being dealt with initially by taxis. In two-thirds of the cases the contents were bowel, which was viable in each case. In one-third omentum only was in the sac. There was no associated immediate mortality, and only 1 case had recurred at the end of 3 years. This is, relatively, a very small number of strangulated herniæ and, in fact, the proportion is one-fourth of that in the Whiston Hospital series (*see* footnote, p. 236)—evidence of the way in which the surgical emergencies go to the regional hospitals rather than to the teaching group.

Mortality.—There were 7 deaths within 3 months of operation (1122 operations in all). All were in men over 50 years old.

1. Two deaths were due to coronary thrombosis :—

a. A man, aged 51 years, died suddenly the day after his discharge from hospital, post-mortem revealing a coronary thrombosis.

b. On the third day after operation a man aged 58 years, with a history of angina pectoris, died suddenly. There was no post-mortem examination.

2. Two more deaths were due to chronic cardiac disease :—

a. A man, aged 66 years, with auricular fibrillation, suffered an embolism of his right superficial femoral artery after the repair of his strangulated hernia. The leg became gangrenous, and he died 6 weeks after operation.

b. Another patient, aged 57 years, compelled to submit to the repair of his hernia owing to its strangulation, made a good recovery but died 3 months later from congestive cardiac failure.

3. The remaining 3 patients died from pulmonary infection:—

a. Two months after his operation under local anæsthesia, a patient with chronic bronchitis died at home from an exacerbation of his infection.

b. The great size of his hernia necessitated repair, which was followed by the death of this patient, aged 67 years, from pulmonary infection 3 weeks later.

c. A man, aged 84 years, had his very large hernia repaired at the same time as his penile carcinoma was removed. He died 10 days later from pulmonary infection.

Only the last two of these deaths can be attributed to the operation, although *Case* 1*b* might have been due to pulmonary embolism (really a most unlikely supposition). The repair of an inguinal hernia other than one which is either strangulated or of massive size is a very safe operation in a patient free from intercurrent disease.

DISCUSSION

Looking back over the 1000 cases the outstanding finding is that this number—even with an 82 per cent follow-up—is not enough to give a dogmatic answer to the question of which technique of those used in the series yields the most satisfactory results. This report is, however, a preliminary one, with the main object of laying down the criteria for the production of comparable statistics for the results of inguinal hernia repair. As a secondary object, an effort has been made to lay down basic statistics with which other results may be compared. The setting out of the preliminary results has been merely an incidental illustration of how the scheme is working. A further 1000 cases are already registered, and many already reviewed, whilst a third 1000 cases will probably need to be added to answer the question above. With this reservation, it *is* possible to draw some conclusions from the findings.

1. The study of the possible factors associated with recurrence shows the deterioration of the results of operation with increasing age and worsening of physique, while heavy work after operation has no obvious ill effects.* Probably this last finding is accounted for by the fact that men habitually carrying out physical work have better muscles than those engaged in sedentary occupations. The inference appears to be that the better the musculature, the better the repair, with the further suggestion that the condition of a patient's muscles (and, consequently, the strength of his repair) is more important than the strain to which the repair is subjected after the operation.

2. The findings with regard to sepsis and chronic sinus formation are disturbing. Improvement might be possible in several ways.

a. It is very probable that infection enters after the operation along a stitch hole, particularly if a hæmatoma has formed beneath the skin, or along the track when the latter has drained or been drained. Sweat-glands are particularly active in this area, and no doubt organisms lie within their ducts and escape the skin sterilization before or at the operation. The usual sealing of the wound beneath adhesive plaster *may* be unwise; perhaps the wound should be dressed more frequently, with the maintenance of the sterility of the skin via applications of spirit at each dressing, until the sutures are out and the stitch holes closed.

b. Routine antibiotics might be the answer. Two series of cases are at present being compared, one with and one without post-operative penicillin systemically. Probably more important is the active treatment of subcutaneous hæmatoma by aspiration and antibiotic cover, if one should occur.

c. Probably most important of all is to bury the nylon (or mersaline) deeply. It is not wise to use it for the external oblique layer, and it is doubtful whether catgut is not just as good for this layer. Where the external oblique strip is long enough to suture partially the external oblique aponeurosis it would be better to avoid nylon for the fixation suture in this layer. A further objection to nylon for the external oblique is the experience of 2 patients who found a nylon knot so uncomfortable beneath the skin that they insisted on its removal in each case. Nylon and mersaline owe their popularity to the fact that it is believed that where these materials are used in hernia repairs the supervention of infection does *not* lead to a chronic sinus, as it used to do so often when silk was used. As this is not true, the advantages of silk need new consideration. Certainly, silk stimulates surrounding fibrosis far more than the new non-irritant materials, and should therefore yield a more sound repair.

3. With regard to the technique of repair, the best one will obviously be that which not only yields the lowest recurrence rate, but which also has a low morbidity rate, especially as regards the spectre of the chronic sinus.

a. In the older patient, serious consideration should be given to a complete closure of the canal. There can be little doubt that more frequent performance of this operation would improve the results at an age when the sacrifice of one testicle is scarcely a calamity. One old man, however, complained bitterly of the removal of a testicle during the repair of his inguinal hernia as he was impotent afterwards—a fact which he attributed to his unilateral orchidectomy. Incidentally, his permission for orchidectomy had not been obtained. Fortunately, litigation was avoided. Even in bilateral cases a division of the cord

* Admittedly, this statement is not supported by one's usual experience in surgical clinics, where a high proportion of men attending with recurrent herniæ are young men occupied in heavy manual work. The explanation is that these men cannot work satisfactorily whilst wearing a truss, and request a further operation. The older men and those engaged in lighter occupations obtain a truss from their doctor without returning to hospital.

could be tried on one side initially, as it might not result in any apparent testicular disturbance. On the results so far, however, it would seem usually preferable to remove the testicle rather than merely divide the cord. A further alternative would be to return the testicle to the abdomen, thus preserving the internal secretion.

Table XII.—Group of Cases of Hernia Repaired by Conservative Method

Period of Follow-up (years)	Age-group (years)			
	16–30	31–45	45–60	61+
1–3	6	10	10 (2 recurrences)	1
3–6	11	8	4	0
6–10	5	16 (1 recurrence)	11	0
10–13	0	5	0	0

b. In the middle-aged groups, the McArthur repair yields good results, free from disability afterwards. The Bassini procedure with nylon or mersaline gives better results, but the shadow of the chronic sinus lies over this method. The W.A. II method has been followed by the best results of all, and this, too, has the least danger of the chronic sinus. The only objections to the acceptance of its good results are the smaller numbers, and the fact that it has not been tested by the registrars to anything like the extent of the others.

c. In young men, the 'conservative' operations have a marked attraction. They leave unharmed the normal mechanism of closure of the canal so that a direct recurrence afterwards is very rare. Interference is slight, so that complications such as post-operation pain, testicular atrophy, and hydrocele, and even sepsis are rare. Nevertheless, in the present series comparatively few (only 22 out of 113 oblique herniæ in the 16–30 years age-group) have had a conservative operation, so that the good results do not carry weight. In the Whiston Hospital series, one group of cases repaired by a conservative method is noteworthy (*Table XII*).

Of the 60 cases repaired over 3 years previously, only 1 had recurred, and that despite the fact that the *average* period of follow-up was over 6 years. Admittedly, the vagaries of statistics are demonstrated by the fact that in a further 27 cases examined less than 3 years after operation there were 2 further recurrences, but both these patients were over 45 years old. Admittedly, too, cases were selected, representing those of moderate or good physique, but they did embrace nearly three-quarters of the series done by one particular surgeon. For an average follow-up of 5 years, they yield a recurrence rate of 1 in 61 for patients under 45 years of age, more than half of whom were heavy manual workers; these are good results by any standard.

The type of conservative operation employed is one described by Kocher (1903) in his text-book on operative surgery. It consists in the exposure of the sac at the external ring—its invagination and transposition far laterally—to be brought out through the abdominal muscles and fixed there with a single suture of twist silk, the redundant sac being cut away. Interrupted catgut sutures burying the silk suture and invaginating the external oblique over the length of the inguinal canal completes an essentially conservative type of repair. This operation was carried out at the Northern Hospital, Liverpool, by the late Mr. J. H. Rawlinson for many years, but unfortunately it now appears to have been abandoned there. It may well be that this is the best operation for the young patient, or, indeed, for any patient with reasonable muscles at least up to 45 years of age.

SUMMARY

A scheme for the clinical study of inguinal hernia repair is described, and the results of the first 1000 cases presented. The difficulties of the study are discussed in detail.

Certain suggestions are made with regard to variation of the operative technique in accordance with the age and physique of the patient. The dangers of infection, especially where non-absorbable sutures of a foreign material are used, are stressed.

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THE RADIO-OPACITY OF GLASS FOREIGN BODIES

WITH REPORT OF A CASE OF INJURY OF THE CAUDA EQUINA BY FRAGMENTS OF GLASS

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The radio-opacity of glass retained as a foreign body seems to be a neglected topic, no major paper having been published since that of Lewis (1932). Only one previous case of glass penetrating the theca is reported (Topliff and Daly, 1931). The present case describes penetration of the sacral theca by indriven glass fragments in a girl aged 7 years.

Fig. 273.—Localized anteroposterior view of upper sacrum showing the opacities.

CASE REPORT

A girl aged 7 years was a victim of an accident during Christmas festivities. She fell on an upright wine glass, in a confined space between a desk and the wall in a corner of the room, so that her spine was acutely flexed. She was fully clothed, but sustained a deep wound over the lumbosacral interval. The wound was sutured in the casualty department of a local hospital and the patient sent home. She was admitted again 48 hours later with acute retention of urine, which dated from the accident. This persisted after catheterization and there was constipation with occasional fæcal incontinence in addition. Mr. R. A. Mogg, to whom she was referred for treatment of the bladder, appreciated that she had a cauda equina lesion. A cystometrogram confirmed that the retention was neurological and not psychogenic, as had first been suspected. She was transferred to the Department of Neurology under the care of Dr. J. D. Spillane. The only signs beyond the dribbling incontinence were a transversely disposed comma-shaped wound and a little perineal hypo-algesia.

The following were found on radiological examination:

1. A general survey film of the abdomen showed an ill-defined linear opacity in the midline, overlying the first sacral vertebra.

2. In a localized anteroposterior view of this region the opacity was seen very clearly, with a second similar shadow lying parallel to it (*Fig.* 273).

3. Lateral radiographs did not show these linear shadows, but anteroposterior tomograms indicated that they lay within the spinal canal.

4. A lumbar myelogram showed an abnormality of the sacral sac, which was deviated to the left and terminated at the lower margin of the first sacral body. A linear filling defect was seen obliquely crossing the lower end of the sac adjacent to the opacities and continuing their line upwards and to the left (*Figs.* 274, 275).

It was concluded that two fragments of glass were present in the sacral canal at the level of the first sacral body, with secondary deformity of the sacral meninges.

Laminectomy was performed by Mr. Charles Langmaid, who found two pieces of glass lying side by side (flat surfaces in contact), with their longest axis in the anteroposterior plane (*Fig.* 276). They were embedded in scar tissue and densely adherent to the dorsal aspect of the theca, but no cerebrospinal fluid escaped when they were removed. On opening the theca above this level it was found that the roots all entered the mass of fibrous tissue in which the glass had been found, and it was not deemed wise to attempt to dissect them free.

When seen recently, 16 months after the accident, the patient was well and back at school. The act of micturition occurred normally and by emptying the bladder frequently and regularly she was able to avoid any episodes of incontinence. She had normal bowel control. The sensory loss was still present.

DISCUSSION

Spinal Lesion.—Traumatic lesions of the spinal cord and cauda equina due to penetrating wounds without vertebral involvement are not common. Almost all reported have been the result of stabbing, a review by St. John and Rand (1953) mentioning 93 such cases up to 1910 and many since then. Castillo and Kahn (1950) record a case in which the broken-off end of a knife-blade was retained for 20 years before progressive disability led to exploration; the rusty blade had transfixed the thoracic cord. Lambert Rogers (1942) removed the eye end of a sewing-needle from the cauda of a man aged 21 years whose back had been penetrated by the needle 17 years before and who had only recently developed sciatica.

There is no mention of such an injury due to glass in Moritz's book on the pathology of trauma (1942), but in relation to stab injuries the point is made that the force of the thrust may so distort the shape of a part that deep lying structures may be brought within reach of quite short blades. A comprehensive American book on forensic medicine (Gonzales, Vance, Helpern, and Umberger, 1954) mentions wounds in other parts due to accidental falling against glass, and states that such wounds are usually comma-shaped.

A case somewhat comparable to the present one is that of Topliff and Daly (1931). This was a child

of 2 years who fell on a glass lampshade and sustained a wound in the loin. This poured fluid, leading to the suspicion of a renal fistula; however, methylene blue given by mouth or injection was not excreted through the 'fistula'. A probe passed up the track

FIG. 274.—Anteroposterior myelogram showing abnormality of the sacral sac and linear filling defect.

FIG. 275.—Lateral myelogram showing abnormality of the sacral sac and linear filling defect.

was found on radiographic examination to have entered the spinal canal between L.2 and 3. Two pieces of glass were removed from the wound without a formal laminectomy being performed, and there was no further leakage of fluid. The child recovered completely.

The explanation for the penetration of the deeply placed and well protected theca, in the present case, lay in the position of the patient at the moment of entry of the glass. With the spine hyperflexed the spinous processes would be separated and the theca brought as superficial as possible. The neurological lesion was presumably the result of severed roots, as it came on immediately. Probably a severe arachnoiditis ensued, which was responsible for the myelographic picture found many weeks after injury.

Radiological Aspects.—Lewis (1932), writing on the visibility of glass as a foreign body, made this statement: "The literature on the localisation of foreign bodies in general is singularly silent regarding glass, though much has been written on the roentgenological localisation of metals such as bullets, shrapnel, etc., and of a variety of small objects that can be swallowed or inhaled." This statement is equally true to-day. There are relatively few recorded instances of glass fragments identified in human tissues radiographically, and none of glass in the spinal canal. Most descriptions of glass are of objects swallowed and held up in the œsophagus, some of glass in the eye.

Lewis suggested that for practical purposes glass could be classified into two main groups. First, 'ordinary' glass, including most of the glass likely to

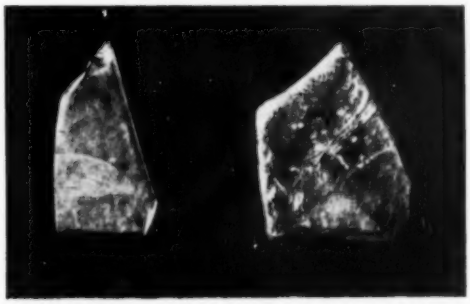

FIG. 276.—Fragments of glass removed from theca. (× 2·625.)

be encountered as a foreign body, and secondly lead or barium glass. To ascertain the effect of overlying soft tissues on the radio-opacity of glass from these two groups, he experimented with paraffin blocks of various thicknesses in which sample fragments were embedded. He concluded that 'ordinary' glass should be demonstrable anywhere in the limbs clear of bone, but in the abdomen only in very favourable circumstances. Lead or barium glass fragments, even if smaller than 2 mm. diameter, should be visible anywhere in the soft tissues or body cavities

if projected clear of bone, provided that the intestinal densities are not great and the patient not too heavy.

Inquiries into the current uses of various types of glass (Douglas, 1957) show that 'ordinary' glass is soda-lime-silicate glass and is used for windows, mirrors, windscreens, and bottles. Lead is used in the foot tubes of electric light bulbs (a flat piece of glass enclosing the base of filament wire), in optical glass, and in X-ray absorbing glass screens. Barium is sometimes used in foot tubes and also in some television tubes. As far as tableware is concerned there are three qualities:—

1. Full crystal glass used for the highest quality hand-made ware. This contains approximately 30 per cent lead, and has a relative density of 3–3·1.

2. Semi-crystal glass containing 16–22 per cent lead, with a relative density about 2·8.

3. Soda-lime-silicate glass containing no lead, and with a relative density of about 2·5. This is used to-day for making cheap wine glasses by automatic machinery.

Thus, in any case in which it is suspected that glass may be retained, an opinion may be formed as to the likelihood of the possibility of demonstrating it radiographically. This may depend on knowing the source of the glass and therefore the type it is likely to be, but if any fragments are available an estimation of the relative density will confirm this.

In the case reported here it was known that the glass was a cheap one purchased at a multiple store. Accurate measurement, using a 10 c.c. specific-gravity bottle, gave a relative density of 2·4. There was no doubt that it was 'ordinary' (soda-lime-silicate) glass, of low radio-opacity. That it did prove possible to identify it radiographically probably depended on its position and the fact that the patient was young and thin. In the anteroposterior projection also the greatest diameter of the fragments was 'end-on' to the incident beam and was thus visible despite superimposed bone.

SUMMARY

1. A case of penetration of the sacral theca by indriven glass fragments is described, with radiological and operative details.

2. The uses and distribution of different types of glass are discussed together with their relative radio-opacity. If the source of any glass is unknown its type may be determined by measuring the relative density.

3. The glass in this case was of the least radio-opaque type, but was visible because the fragments were end-on in the standard anteroposterior views.

Acknowledgements.—We are grateful for permission to publish this case to the clinicians successively responsible, Mr. Richard Mogg, Dr. J. D. Spillane, and Mr. Charles Langmaid; and to Dr. E. H. Hanson, Director of the Department of Radiology. Professor R. W. Douglas of the University of Sheffield advised us about the properties and uses of glass. We thank also the radiographic staff of the Cardiff Royal Infirmary, and Mr. R. Marshall for the photographs. Mr. R. G. Wood, Principal Physicist at the Radiotherapy Hospital, Whitchurch, kindly carried out the estimation of relative density.

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THE OCCURRENCE AND SIGNIFICANCE OF STAPHYLOCOCCUS AUREUS IN THE FÆCES*

AN INVESTIGATION IN SURGICAL WARDS

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THERE are difficulties in accepting the theory that necrotizing enteritis is due to the enterotoxin of an antibiotic-resistant *Staphylococcus aureus*. This organism may flourish where the normal intestinal flora have been wholly or partly suppressed by the use, especially by mouth, of broad-spectrum antibiotics, and is found in unusual numbers in the stools of the majority of victims. It is suggested that in this way the antibiotics are responsible for the disease.

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In a recent article on the subject of necrotizing enteritis (Pullan, 1955) the significance of *Staph. aureus* found in the stools of some of the victims was questioned. In the first place, not much was known of its incidence in the normal intestine, or of the frequency of its appearance, or its resistance to antibiotics in the stools of those patients without gastro-intestinal symptoms who were receiving various forms of antibiotic treatment in hospital. In addition, there is the difficulty of understanding those undoubted cases of fulminating necrotizing enteritis in which staphylococci could not be found

in the fæces, and those in which neither antibiotic nor chemotherapy had been given (Williams and Pullan, 1953; Dawson-Edwards and Morrissey, 1955). Furthermore, the frequency of this disease was thought by Kleckner, Bargen, and Baggenstoss (1952) not to have increased since the discovery of chemotherapy and antibiotics.

In those patients who contract necrotizing enteritis after antibiotic treatment and in those who do not, it is not surprising that the stools should contain organisms resistant to that antibiotic (provided that the antibiotic can reach their habitat), though they may not necessarily be implicated in an aetiological role. In this connexion Oeding and Austarheim (1954) showed that 26 per cent of a series of patients who died from various causes (not necrotizing enteritis) after antibiotic therapy, harboured *Staph. aureus* in the intestine, as compared with 17 per cent of those dying without previous antibiotic treatment. The staphylococci existed more abundantly in the upper small bowel, and their resistance to antibiotics increased the farther down the bowel they were found. The authors stated that "a number of persons not treated with antibiotics and persons treated but without gastro-intestinal symptoms have staphylococci, occasionally in abundance, in their intestine".

In other words, the evidence that *Staph. aureus* is the causal agent of necrotizing enteritis may be no more than circumstantial.

The present investigation was designed to discover:—

1. The frequency and types of *Staph. aureus* in the stools of the normal population.
2. The change in incidence and type as a result of (*a*) hospitalization; (*b*) antibiotics; (*c*) operation.

MATERIAL

The investigation was carried out in three wards, on all new non-urgent admissions to the surgical team, whose stay seemed likely to be long enough for investigation. The following material was examined:

1. The first stool passed in hospital.
2. A stool two or more days after operation, or, if there was no operation, at approximately half-way through the hospital stay. Sometimes additional specimens were also examined.
3. A stool a day or two before discharge.
4. Nose swabs within 24 hours of admission and a day or two before discharge.

[The actual laboratory work was carried out exclusively by one of us—H. G. P.]

METHODS

1. Collection.—Specimens of stool were collected and kept in wax cartons and with few exceptions were examined within 48 hours. Nose swabs were made by thorough rubbing of both anterior nares, and cultured within a few hours.

2. Culture.—Nutrient agar containing 6 per cent NaCl (Maitland and Martyn, 1948) was used as the selective medium for isolating *Staph. aureus* from the fæces, and for convenience the same medium was also used for nose swabs. The stool was plated out sufficiently heavily to leave visible particles. All salt-agar cultures were incubated at 37° C. for 48 hours. A culture on MacConkey's medium and a Gram-stained film were also made from each specimen of fæces.

3. Identification of Staph. aureus and Selection for Sensitivity Testing.—Subcultures on to agar slopes were made from staphylococcal colonies that were not perfectly white after incubation and 24 hours at room temperature. Primary stool cultures showing only one or two colonies of staphylococci were ignored (*see also* Discussion), but when more were present up to three per plate were subcultured. A single colony was selected unless the colonies were numerous or differed in appearance. Those strains that were coagulase-positive by the tube method (Fisk, 1940) were then tested by the ditch plate method for sensitivity to the following antibiotics, in the concentrations given: penicillin 10 U/ml. (*P*); oxytetracycline, 100 μg./ml. (*O*); chloramphenicol, 50 μg./ml. (*C*); streptomycin, 50 μg./ml. (*S*), and except in a few earlier cases, erythromycin, 50 μg./ml. (*E*). Staphylococcal sensitivity to oxytetracycline has been taken as representative of that to the whole tetracycline group (Barber and Burston, 1955). The standard Oxford staphylococcus was used on each plate as a sensitive control. Three grades of reaction to antibiotics were recognized: S, fully sensitive; R_1, partially resistant (i.e., growing significantly nearer the antibiotic ditch than the Oxford staphylococcus, but not actually over it); R_2, fully resistant (i.e., growing over the ditch).

In this work the sensitivities of all staphylococci on any one plate have been assumed to be the same as in the few colonies actually tested. This is a necessary assumption, but its validity tends to be confirmed by finding the same sensitivities in each of two colonies in the 48 cases in which paired tests were done, and minor differences in sensitivity in only one of five plates in which triplicate tests were made. Hereafter *Staph. aureus* should be taken to mean coagulase-positive *Staph. aureus*.

4. Phage Typing.—Certain selected strains were next phage-typed at the Staphylococcal Reference Laboratory at Colindale (through the kindness of Dr. R. E. O. Williams).

RESULTS

One hundred and nineteen patients were studied, though information is not complete in all cases.

1. Stools.—*Table I* shows the incidence of *Staph. aureus* in the stools in routine cases of admission to hospital.

Table I.—STAPH. AUREUS IN STOOLS OF ROUTINE ADMISSIONS

	No. of Patients tested	*No. carrying Staph. aureus*	*Per cent* (approx.)
1st stool after admission	89	8	9
After 1st week	70	10	14

This apparent increase is probably deceptive, because a patient on admission is classified on a single sampling, whereas the incidence of subsequent positives is obtained by a combination of several samplings, so that a patient whose stool has later been cultured four times is counted as a positive, although three of these cultures may, in fact, have

been negative. In other words, the more frequently the stools of a patient are tested the more likely is *Staph. aureus* to be found.

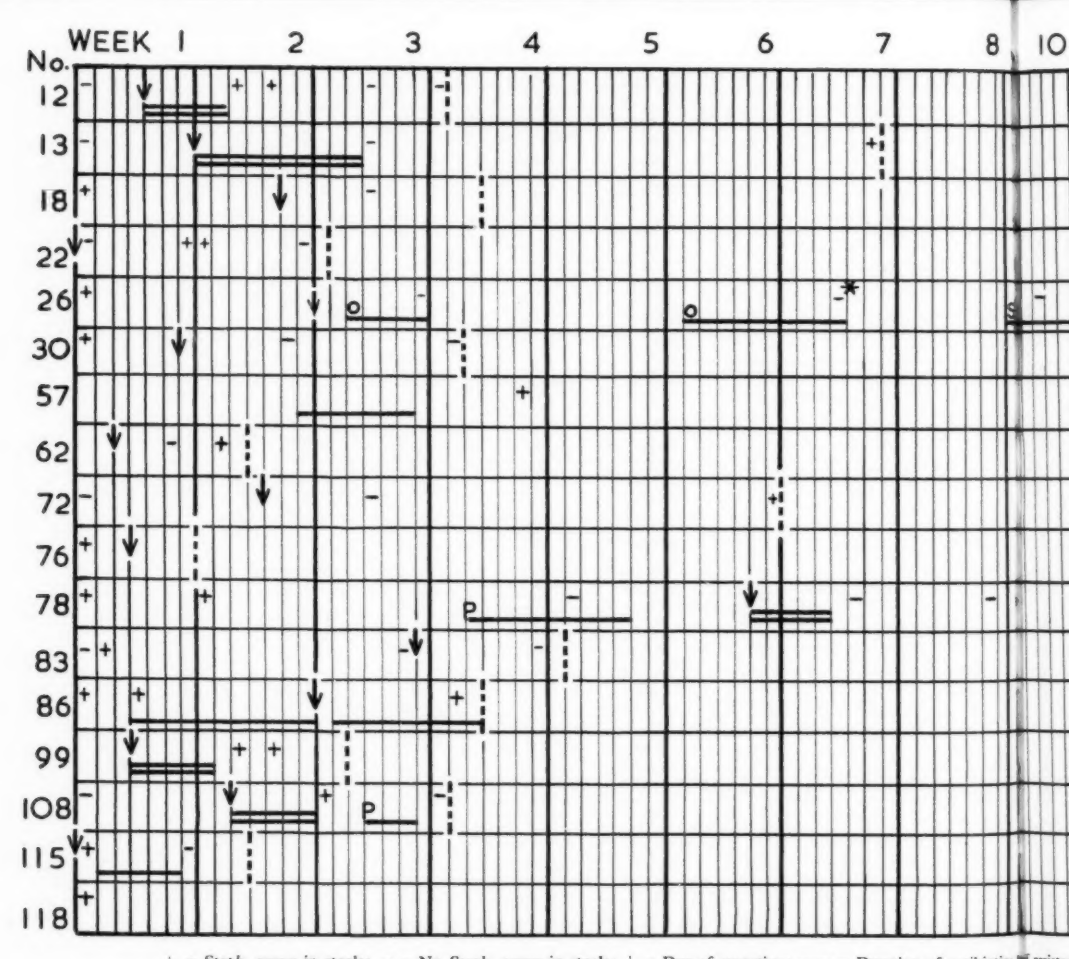
Staph. aureus was found in the stools of seventeen patients in all (1 patient being positive both on admission and subsequently). *Table II* shows the timing of these positive cultures in relation to operation and the administration of antibiotics or sulphonamides.

None of these patients complained of diarrhœa. Heavy growths of *Staph. aureus* were obtained in only three instances (in 1 patient on admission), but in all three coliforms appeared in normal numbers on MacConkey's medium, and the Gram-stained films from the fæces were not remarkable. Nevertheless, the stools of two of the three patients were loose. In no case was the normal fæcal flora altered as a result of antibiotic treatment, which was in most cases parenteral.

The seventeen cases thus represented are analysed further in *Table III*.

The stools of 8 patients were found to contain *Staph. aureus* on admission. Of these 8 patients 2 escaped further investigation; 1 continued to harbour *Staph. aureus* throughout her hospital stay, though changed after administration of oxytetracycline to a resistant strain ($P_{R_1}O_{R_2}C_S S_{R_3}E_S$). (This patient therefore appears under two headings in

Table I... CULTU...



+ = *Staph. aureus* in stools; − = No *Staph. aureus* in stools; ↓ = Day of operation; —— = Duration of antibiotic; ... resista...

C = Chloramphenicol; *E* = Er...

Table III); 2 lost the *Staph. aureus* though receiving no antibiotics; 3 lost the *Staph. aureus* after receiving antibiotics to which the particular organism was sensitive.

Influence of Operation and Antibiotics on the Appearance of Staph. aureus in the Stool.—Table IV shows the distribution of positive cultures in the various groups of cases. The column showing the positive cultures excludes those that were found to be positive on admission only.

The addition of antibiotics does not appear to have increased the incidence of fæcal staphylococci occurring after operation.

It is noteworthy that of the 6 patients who had resistant (Group C) staphylococci in the stools 5 had had operations on the stomach or duodenum (with antibiotics), out of a total of 11 operations of this type. In this group of operations the incidence of fæcal staphylococci was very little less than in some published series of necrotizing enteritis cases and greater than in some.

In 3 patients (2 gastrectomies and 1 choledochojejunostomy) cultures were taken at operation from jejunum in all 3 and stomach in 2. *Staph. aureus* was not found, although it was present in the nose of one of the patients 3 weeks before operation, and in the nose of 2 and stools of 1 of them between 2 and 6 weeks after operation.

Table IV. CULTURES

8	10	11	Diagnosis, Operation, and Antibiotic Treatment	Nasal *Staph. aureus* at Any Time	Sensitivities					Gastro-intestinal Symptoms
					P	*O*	*C*	*S*	*E*	
			Duodenal ulcer. Partial gastrectomy. Penicillin and streptomycin (parenteral)	Yes	R_1	R_2	S	R_2	S	No
			Carcinoma of pancreas. Cholecystjejunostomy. Penicillin and streptomycin (parenteral)	Yes	R_1	S	S	R_2	S	No
			Goitre. Partial thyroidectomy. No antibiotics	Yes	R_1	S	S	S		No
			Cholelithiasis. Cholecystlithotomy. No antibiotics	Yes	S	S	S	S	S	No
			Bronchopleural fistula. Lobectomy. Oxytetracycline (oral) and streptomycin (parenteral)	Yes	S	S	S	R_2		Yes
			Myasthenia gravis. Thymectomy. No antibiotics	No	S	S	S	S		No
			Chronic osteomyelitis. No operation. Erythromycin (oral)	No	R_2	R_1	S	R_2	S	No
			Spermatocele. Excision. No antibiotics	No	S	S	S	S	S	No
			Coarctation of aorta. Graft. No antibiotics	Yes	R_1	S	S	S	S	No
			Hiatus hernia. Œsophagoscopy. No antibiotics	Yes	S	S	S	S	S	No
			Carcinomatosis. Adrenalectomy. Penicillin and streptomycin (parenteral)	Yes	S	S	S	S	S	No
			Goitre. Thyroidectomy. No antibiotics	Yes	R_1	S	S	S	S	No
			Carcinoma of stomach. Palliative resection. Oxytetracycline (oral)	Yes	S R_1 R_2	S S R_2	S S R_1	S S R_2	S S S	No
			Peptic ulcer. Partial gastrectomy. Penicillin and streptomycin (parenteral)	No	R_1	R_2	S	R_2	S	No
			Duodenal ulcer. Partial gastrectomy. Penicillin and streptomycin (parenteral)	Yes	R_2	R_2	S	R_2	S	No
			Strangulated hernia. Repair. Penicillin (parenteral)	No culture	S	S	S	S	S	No
			Duodenal ulcer. No operation. No antibiotics	Yes	R_1	S	S	S	S	No

ntibiotic; [illegible] resistant coagulase-negative *Staph. albus* and *Proteus vulgaris*; ¦ = Discharge ; *P* = Penicillin; *O* = Oxytetracycline ; mphenicol; *E* = Erythromycin.

Influence of Antibiotics on Incidence of Carrier State and Type of Organism.—This includes only those cultures obtained 4 days, or later, after the beginning of antibiotic therapy, or more than a week after admission in those patients not given antibiotics.

Table V again shows the increase in proportion of resistant strains in nose and stool after antibiotics. The carrier incidence is scarcely affected.

2. Nose Swabs.—The following figures are quoted to show the general background of nasal staphylococci infections against which the fæcal strains were found.

Nose swabs were taken and cultured in 105 cases, within the first 24 hours; 31 (30 per cent) yielded *Staph. aureus*, but only 2 gave Group C resistant strains; in both instances the patients had already recently been in hospital.

Table III.—Effect of Antibiotics on Sensitivity of Staphylococci in Stools

Patients	Total	Sensitive to All Antibiotics (Group A)	Some Resistance to One Antibiotic (Group B)	Resistant to Two or More Antibiotics (Group C)
With *Staph. aureus* in stool on admission	8	6	2	0
Acquiring *Staph. aureus* after antibiotics	6	0	0	6*
Acquiring *Staph. aureus* without antibiotics	4	2	2	0

31 patients had received antibiotics but no *Staph. aureus* was found in their stools

* One patient, after erythromycin treatment, grew *Staph. aureus* which was sensitive to erythromycin, though the other 5 patients had strains resistant to the particular antibiotics given.

Table IV.—Distribution of Positive Cultures

	No. of Patients	*No. with Positive Stool Cultures*
Operation and antibiotics	54	5
Operation and no antibiotics	47	4
Antibiotics and no operation	4	1
No antibiotics and no operation	14	0

Table V.—Influence of Antibiotics on Carrier State and Organism

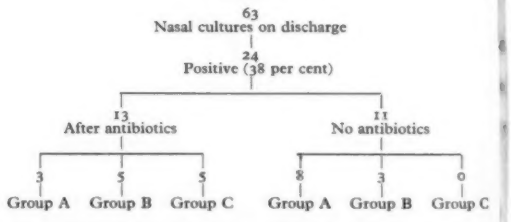
	Totals		Group C	
	Nose	Stool	Nose	Stool
No. not receiving antibiotics and who were cultured later	29	33		
Staph. aureus found	11	4	0	0
per cent	38	12		
No. receiving antibiotics and who were cultured later	34	37		
Staph. aureus found	13	6	5	6
per cent	38	16		

Of 74 patients whose nasal swabs were negative on admission 9 patients subsequently became positive. Of these 7 acquired penicillin resistant strains and 2 acquired penicillin sensitive strains (only 63 retested).

In addition 4 patients (positive on admission) changed their sensitive strain for a Group C resistant one. Three of the four had taken various antibiotics, and in each case the subsequent organisms proved resistant to the antibiotics used.

Table VI shows the situation on discharge and the effect of antibiotics on the sensitivities of the staphylococci found in the nose at this time. The carrier rate rose from 30 per cent to 38 per cent.

Table VI.—Effect of Antibiotics on Staphylococci in Nose



3. Correlation between Staph. aureus in Nose and in Stools.—Forty-two patients had positive nasal cultures. Of the 31 positive on admission, 10 at some time grew *Staph. aureus* in the stool (as compared with 30 out of 63 in Brodie, Kerr, and Sommerville's (1956) series).

Of 9 originally negative, but becoming positive, 2 at some time grew *Staph. aureus* in the stool.

Of 65 originally and subsequently negative, 4 grew *Staph. aureus* in the stool.

Twelve of the 17 patients with positive stool cultures harboured a nasal *Staph. aureus* at one time or another (one not tested). It was a demonstrably different one in 7 cases and similar in 5. By comparison, 90 patients had negative stool cultures, and of these 30 were nasal staphylococcus carriers. On admission 8 patients who had positive stool cultures also had nose swabs taken; 5 of the 7 tested were nasal carriers of *Staph. aureus*. Comparison of nasal and fæcal strains from some patients is shown in *Table VII*.

Of all staphylococci phage-typed (36) the resistant (Group C) strains (12) were confined to phage-group III, while the sensitive (Group A and B) strains (24) were distributed amongst all 3 phage groups. Three of Group C and 1 of Group B were untypable. This distribution is a usual finding (Barber and Whitehead, 1949; Rountree, Barbour, and Thomson, 1951), though more recently resistant strains have appeared

Table VII.—Correlation between Nasal and Fæcal Staphylococci in 9 Patients
(Stool specimens obtained not later than 4 days after nasal swab)

	Source	Sensitivity					Phage Type	Group	Correlation
		P	*O*	*C*	*S*	*E*			
On admission	Nose	R_1	S	S	S		Untypable		Doubtful
	Stool	R_1	S	S	S		79	I	
	Nose	S	S	S	S	S	52	I	Same
	Stool	S	S	S	S	S	52	I	
	Nose	R_1	S	S	S	S	52A/79+	I	Different Replaced by 52A/79 R_1 S S S S 4 days later
	Stool	S	S	S	S	S	52/52A/79/80/7/42E/47/53/54	I and III	
	Nose	S	S	S	R_2		52A/80+	I	Same
	Stool	S	S	S	R_2		52A/80+	I	
	Nose	S	S	S	S	S	73	III	Doubtful
	Stool	R_1	S	S	S	S	73. Very weak reaction	III	
On discharge	Nose	R_2	S	S	R_2	S	6/47/75/77	III	Same
	Stool	R_2	S	S	R_2	S	6/47/75/77	III	
	Nose	R_1	S	S	S	S	6+. Weak reaction	III	Same
	Stool	R_1	S	S	S	S	6+. Weak reaction	III	
During hospital stay	Nose	S	S	S	S	S	3B/3C/55/71	II	Different
	Stool	R_1	S	S	S	S	73+	III	
	Nose	R_1	S	S	S	S	52A/79+	I	Same
	Stool	R_1	S	S	S	S	52A/79+	I	

in Groups I and II. Group III contains most of the enterotoxin-producing staphylococci (Allison, 1949) and is the group most frequently found in normal fæces (Williams, Rippon, and Dowsett, 1953).

Frequency of Various Sensitivity Patterns in the Strains of Staphylococci isolated.—*Table VIII* shows the number of organisms in the various sensitivity groups and the numbers of patients from whom these varying types were obtained. This demonstrates the

Table VIII.—Cultures isolated from any Source —Nose, Stool, Wound (8), Sputum (3)

	P	*O*	*C*	*S*	*E*	Total	Patients
Group A	S	S	S	S	S	52	37
Group B	R	S	S	S	S	29	19
	S	S	S	R	S	3	2
Group C	R	S	S	R	S	2	1
	R	R	S	R	S	17	10
	R	R	S	S	S	2	2
	R	R	S	S	R	1	1
	R	R	R	R	S	1	1
	R	R	R	R	R	0	0

present relative rarity of resistant staphylococci in as much as only 1 strain was resistant to 4 of the 5 antibiotics, though another was resistant to erythromycin. There were no organisms resistant to all 5 antibiotics.

It is worth noting (although not shown in the table) that resistance to streptomycin, when it occurred, was nearly always complete.

DISCUSSION

Criticism of the Method.—It has proved difficult to secure complete information on all patients according to the plan of investigation as originally worked out. Cultures have inevitably, though unselectively, been missed or first stools have not been secured from constipated patients for perhaps a week after admission. In this latter case it is difficult to know whether to regard such a specimen as being a stool of admission, or whether it has been possible for a staphylococcus, acquired since admission to the ward, to gain the lower reaches of the bowel by this time. The disregarding of colonies of *Staph. aureus* when there were fewer than three in a stool culture may be challenged. This was done so that the results would not be unduly influenced by organisms originating from outside the bowel, e.g., from the perianal skin. If there were more than two colonies of *Staph. aureus* on the plate there were usually many more. Study of our original records shows that 11 stool cultures (all from patients we have counted as negative) grew only one or two colonies of *Staph. aureus*, 7 of these being obtained on admission. Their antibiotic-sensitivity behaviour was the same as in those counted as positive, but correlation with nasal carriage was less marked.

Carrier Rates.—A staphylococcal carrier rate on admission in the stool of about 10 per cent and in the nose of about 30 per cent does not differ greatly from carrier rates published in certain other works (Barber and Burston, 1955; Brodie, Kerr, and Sommerville, 1956; Cook, Elliott, Elliot-Smith, Frisby, and Gardner, 1957), though at the Staphylococcal Reference Laboratory at Colindale 33 per cent of routine stool specimens contained *Staph. aureus* (Allison, 1949). A nasal carrier rate of up to 60 per cent is quoted by Rountree and Thomson (1949). It has not been possible in the present investigation to show that the carrier rates are, in general, increased as a result of either hospitalization, operation, or the use of antibiotics. The 38 per cent incidence of staphylococcal carriers on discharge compared with 30 per cent on admission is an apparent increase of doubtful statistical significance. However, the incidence of resistant strains both in nose and stool is significantly greater in those patients who have received antibiotics, though the staphylococci cultured on discharge when antibiotics were not given are no more resistant than those on admission. It seems difficult for a resistant staphylococcus to establish itself in nose or bowel without the aid of antibiotics. In the stools, during the period of hospitalization the overall incidence of staphylococci *at any one time* appeared to be about 10 per cent, although the identity of the carriers was consequently changing and no patient carried the same strain of staphylococcus throughout his stay in hospital. Among those patients not receiving antibiotics 2 patients, positive on admission, lost their staphylococci, but 4 others, negative at first, became positive at some stage, though not necessarily remaining so. In the same way, of those patients receiving antibiotics 3, positive beforehand, lost their sensitive staphylococci, though not necessarily as a result of antibiotic treatment, and 4, originally negative, became positive, with resistant strains. Thus, the figure of 10 per cent carrier rate in the stools, at first sight seemingly constant, is compounded of two conflicting trends. On the one hand are those patients entering hospital with a fæcal staphylococcus and subsequently losing it; on the other hand, a second group is staphylococcus-free on admission and acquires it in hospital, though often only temporarily. In the first group the loss of the staphylococcus, sensitive in all instances, might be expected after administration of an appropriate antibiotic, though it also occurred when no antibiotic was given. In the second group the acquired staphylococcus, after antibiotic therapy, was resistant in all cases.

In one series the fæcal carrier rate rose from 17 per cent to 38 per cent (Brodie, Kerr, and Sommerville, 1956), but this was in a dysentery ward where the frequent use of broad-spectrum antibiotics by mouth may have influenced such an increase. In this connexion perhaps we, and others, have paid insufficient attention to whether the antibiotic was received parenterally or by mouth, as the latter route is much more devastating to the intestinal flora. The parenteral administration of such drugs as penicillin and streptomycin (often the only ones received before the onset of necrotizing enteritis) would never be chosen to influence intestinal organisms (e.g., prior to colonic surgery) and, in fact, their effect by this route is usually negligible.

The results show a marked intermittence in the fæcal carriage of *Staph. aureus*, which is much less noticeable in the nose. None of the 17 patients showing positive stool cultures carried the same *Staph. aureus* throughout their stay in hospital, and only one continued positive in all cultures. It is difficult to know how truly this indicates an actual transient carriage of *Staph. aureus* or whether the scantiness of this organism in the stool merely makes its discovery a matter of chance.

Association of Nasal and Fæcal Carriage.—Although we find some correlation between the carriage of *Staph. aureus* in the nose and in the stools, where the organisms from each source in the same person are compared by sensitivity and phage typing, they are more often dissimilar. It seems that certain persons are prone to pick up any staphylococcus present in the environment, rather than become widely colonized by a single strain.

Oeding and Austarheim (1954) found usually identical organisms from different sites in the intestines of a patient, but findings similar to ours are reported by Brodie, Kerr, and Sommerville (1956). In one fatal case of necrotizing enteritis reported by Todd and Hopes (1955) a resistant strain of *Staph. aureus* was recovered from nose and stools, but these differed slightly in their sensitivities. In another series of paired strains from nose and stools of 31 patients, there were the same staphylococcus in 21 cases, and in 4 others identical organisms were collected from throat and stools (Allison, 1949).

Necrotizing Enteritis.—We had hoped to have the opportunity of studying, during the period of this investigation, at least one patient with necrotizing enteritis. No such opportunity presented, however, nor were staphylococci found in the overwhelming numbers which is considered a typical, but by no means invariable, finding in this condition. Although necrotizing enteritis was well known and possibly no less frequent in the pre-antibiotic era (Kleckner, Bargen, and Baggenstoss, 1952), the present hypothesis of its aetiology postulates that the ideal setting for the development of the disease consists of a patient harbouring or acquiring staphylococci, in the gut or nasopharynx, which are resistant to the broad-spectrum antibiotics (particularly oral) which he is receiving, and who undergoes some form of major abdominal—usually gastric—surgery. These prerequisites were fulfilled in only 1 patient (*Case* 68) in the whole of our series, and then only imperfectly, in so far as the antibiotic was administered by injection and not by mouth. No symptoms developed. One other patient grew Group C staphylococci from the nose (*Case* 72) (*see Table II*) prior to operation for coarctation; he received no antibiotics.

It is not difficult to find cases of necrotizing enteritis in which no staphylococci can be found, either in fæces or membrane, by recognized selective techniques. Are these cases due to a hidden staphylococcus or to other causes? In other victims the fæcal flora is not abnormal in the Gram smear even when staphylococci are cultured from the same specimen. Can antibiotic suppression of the residents be a factor here? It is difficult to incriminate the

antibiotics when they have not been given, or when they have only been administered by a route, and are of a type (as in the majority of cases), which only rarely can be shown to alter the intestinal flora of the colon. Surgeons are still searching for an antibiotic which, by any route, gives more than a partial and very temporary control over intestinal organisms. Can the antibiotic suppression of normal flora still be held to be a factor in the disease when the most severe lesions are usually found at a site where there is no normal flora (Cregan and Hayward, 1953; Cregan, Dunlop, and Hayward, 1953; Cook and others, 1957), and where parenteral antibiotics scarcely reach and are very often of a type (penicillin) ineffective against Gram-negative organisms?

It may be that the small bowel is normally kept free of colonic organisms by the speed of the intraluminal stream exceeding the speed of upward bacterial invasion from the colon. Such an invasion readily occurs when the stream is stilled, as after death, or in chronic intestinal obstruction, and might obtain during the usual post-operative intestinal inertia which is almost physiological after major operations such as gastrectomy. If this were the explanation, the severity of the lesion should diminish in proportion to the distance from the ileocæcal valve. This is not the case.

CONCLUSION

It has been shown that *Staph. aureus* sometimes exists in the gastro-intestinal tract of patients both at the time of their admission and during their stay in hospital, and that the incidence does not seem in general to be affected by operation or antibiotics. Some of these strains may be of the resistant type, though these are usually only found in those patients who have received antibiotic treatment. It has also been shown elsewhere that it is not possible in all cases to find staphylococci in the fæces of patients suffering from necrotizing enteritis (Williams and Pullan, 1953; Dawson-Edwards and Morrissey, 1955); also that staphylococci may occur, occasionally in abundance, in the intestines of those who are not suffering from the disease (Oeding and Austarheim, 1954). It still remains to be proved that the staphylococci found in the majority of patients who are suffering from necrotizing enteritis are responsible for the intestinal lesion. Their presence may be no more than coincidental, favoured by the liquid medium (Dolman, 1935) and their ability to resist the antibiotics in use, to the exclusion of more sensitive organisms. When it is more easily possible to test strains of staphylococci isolated from these cases for enterotoxin production, some of the present disparity between symptoms caused and the presence of the organisms may be more readily explicable (Surgalla and Dack, 1955).

SUMMARY

1. The occurrence of *Staph. aureus* in the stools of hospital patients has been investigated. The carrier rates of staphylococci in the nose and stools of patients on admission to hospital have been found to be approximately 30 per cent and 10 per cent respectively. All three phage groups were represented, but the organisms were, in general, sensitive to antibiotics.

2. Carriage of staphylococci in the stools of hospital patients appears to be intermittent and the more cultures that are examined from any group of patients, the higher will the carrier incidence appear to be.

3. In the whole mixed series of patients, some having antibiotic treatment or undergoing operation, some both, some neither, there was no significant increase in fæcal staphylococcal carriage rate during stay in hospital. The factors contributing to this overall steadiness are discussed.

4. A group of patients acquired fæcal staphylococci of phage-group III, resistant to several antibiotics. All had had antibiotic therapy, and the majority operations involving removal of part of the stomach.

5. No cases of necrotizing enteritis occurred, and the staphylococci, when encountered, were far less numerous than in most cases of the disease attributed to this organism. In no case was the normal flora eliminated as a result of antibiotic treatment.

6. The presence of staphylococci in the stools seems to be correlated with nasal carriage, though not necessarily of the same strain.

7. These results are discussed in relation to the condition of necrotizing enteritis.

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CARCINOMA OF THE PARATHYROID

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THE parathyroid glands are generally believed to have been discovered by Sandstrom, a little more than seventy years ago (Sandstrom, 1880). However, they were first described in the rhinoceros by Richard Owen in 1852, the year of Sandstrom's birth (Cave, 1953). In the closing decade of the nineteenth century they were rediscovered by Gley (1891), and this worker, as well as Vassale and Generali (1900) (who gave them their present name), showed that post-operative tetany was due to extirpation of the parathyroid glands, and that the glands played no part in preventing myxœdema. In the years before World War I, Erdheim (1906) showed that the parathyroid glands were concerned in calcium metabolism and were hyperplastic in patients with rickets (Albright, 1948). Meanwhile, a single parathyroid adenoma had been noted in patients with osteitis fibrosa cystica, and in 1915 Schlagenhaufer pointed out that hyperplasia, if secondary and beneficial, should involve all four glands, and postulated a parathyroid adenoma as the cause of the disease (Albright, 1948). These two concepts successively influenced Mandl (1926) in his treatment of a patient with osteitis fibrosa cystica. This patient's symptoms progressed despite the use of extracts of animal parathyroids, and grew even worse after a transplant of human parathyroid. Mandl re-operated and removed a parathyroid adenoma and was able to witness the first recovery from this disease. After this signal success hyperparathyroidism became recognized with increasing frequency; one review of the literature (Norris, 1947) listed more than 300 cases. Workers at the Mayo Clinic (Woolner, Keating, and Black, 1952) could write from their experience of 140 patients, and those at the Massachusetts General Hospital (Cope, Nardi, and Castleman, 1953) from comparable material. More recently 60 cases have been described from Sweden (Hellstrom, 1954), and there have been numerous reports of smaller series.

A few patients with hyperparathyroidism relapse months or years after the removal of the adenoma; this relapse is associated with local recurrence and invasion of surrounding tissues, lymph-nodes, or visceral metastases. Occasionally these findings may be made at the original operation.

Table I.—CHRONOLOGICAL RECORD OF CASES IN THE LITERATURE

VISCERAL METASTASES	LYMPH-NODE METASTASES	LOCAL RECURRENCE	LOCAL INVASION WITHOUT RECURRENCE
Meyer and Ragins (1943)	Gentile, Skinner, and Ashburn (1941)	Gutman, quoted by Snapper (1943)	Fretheim and Lange (1948)
King and Wood (1950)	Black (1948)	Burk (1947)	Maruelle (1950)
Bertrand-Fontaine and Moulonguet (1950)	Massachusetts General Hospital *Case* 34491 (1948)	Young and Emerson (1949)	Anderson and McWhorter (1951)
von Albertini (1950)	de Wesselow and de Wardener (1949)	de Gennes, Simon, Bricaire, and Tourneur (1949)	Woolner, Keating and Black (1952)
Ellis and Barr (1951)	Black and Ackerman (1950)	Stephenson (1950)	
Massachusetts General Hospital *Case* 39101 (1953)	Warner, quoted by Black and Ackerman (1950)	O'Donovan, Meade, and McGrath (1951)	
	Black (1954)	Wray (1953)	

A group of such patients has been collected from the literature (*Table I*). They have been divided into three categories: those showing visceral metastases, those showing spread to lymph-nodes, and those showing invasion of neighbouring tissues.

To these may be added the present patient, from whom a metastasis was removed before the primary tumour was discovered.

CASE REPORT

R. L., a 32-year-old chemist, was referred to the Royal Melbourne Hospital on December 5, 1954.

His illness had begun insidiously, perhaps a year previously. At first he noticed only loss of weight, then undue tiredness and irritability, and later, pains in his legs, especially after much walking or prolonged standing.

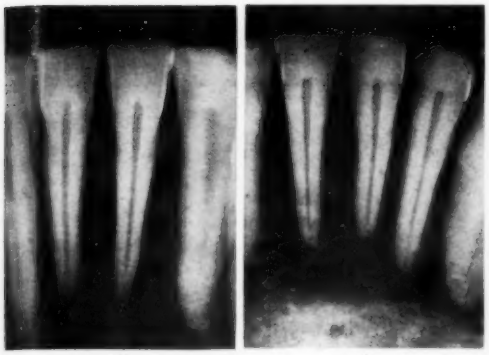
Other symptoms gradually appeared: loss of appetite, burning epigastric pain and flatulence, episodes of vomiting and thirst, frequency, and nocturia.

Finally, he was forced to bed by increasing weakness and repeated vomiting.

ON EXAMINATION.—He was pale and had obviously lost weight. His blood-pressure was 135 mm. of mercury systolic and 95 mm. of mercury diastolic. There was a soft mobile mass about 3 cm. in diameter in the posterior triangle of the neck, behind the origin of the right sternomastoid muscle. His teeth, though sound, were loose in their sockets, and his limbs tender to the touch. His urine showed a trace of albumin; his hæmoglobin was 12·7 g. per 100 ml., his serum calcium 24·8 mg., phosphorus 2·3 mg., and blood-urea 70 mg.

Radiographs showed generalized rarefaction of bone with subperiosteal absorption of phalanges, loss of the lamina dura, and ground-glass haziness of the cranium (*Figs.* 277 279). A barium meal and films of the renal tracts were normal.

The patient was allowed home for Christmas, and was re-admitted on Dec. 28, 1954, extremely ill from a hæmatemesis, which had begun soon after he had eaten his Christmas dinner.



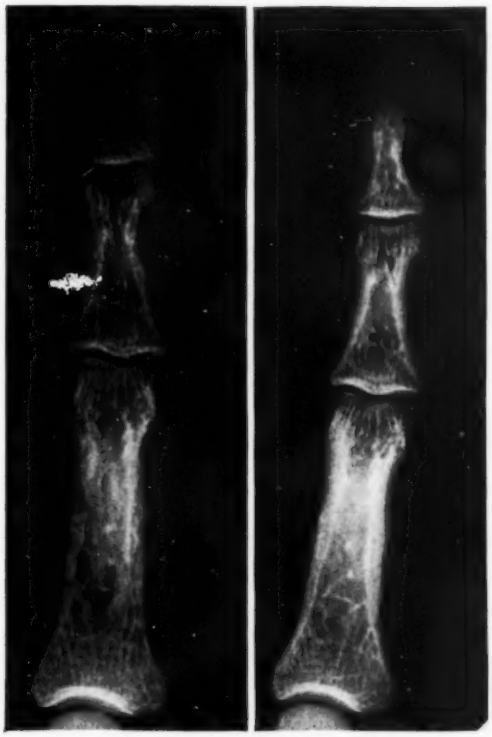
A B

FIG. 277.—Radiograph of lower incisor teeth, showing absence of lamina dura pre-operatively and its reappearance 6 months after the second operation.

AT OPERATION.—He was transfused slowly and after his condition had improved, the nodule was removed on Dec. 31 under local anæsthesia. A 2-in. incision was made lateral to the origin of the sternomastoid and the platysma incised. Thereupon, the nodule was easily dislocated into the wound from its position in the posterior triangle, and removed intact.

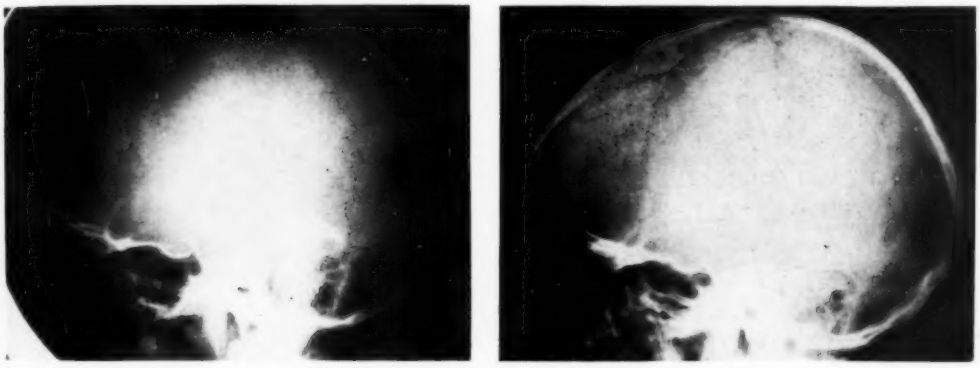
After operation the patient gradually improved and his serum calcium fell to 12·4 mg. The biochemical data for the whole illness are shown in *Fig.* 280.

After his discharge from hospital he failed to gain weight and was still weak and tired. Two months post-operatively his serum calcium had risen to 16·2 mg. per 100 ml. Later, a nodule was palpated deep to the lower portion of the right sternomastoid and on April 21, 1955, the patient's neck was explored under general anæsthesia. A hard tumour 3 cm. in diameter was found behind the lower pole of the thyroid gland. It was adherent to the gland, the recurrent laryngeal nerve, the trachea, œsophagus, and prevertebral muscles. The tumour was



A B

FIG. 278.—Radiograph of phalanges, before operation, and 6 months after second operation. The first film shows rarefaction and subperiosteal resorption of bone; the second, restoration to normal.



A B

FIG. 279.—Radiograph of cranium. Loss of surface markings and ground-glass haziness. Normal appearances post-operatively.

removed with its capsule, the nerve being sacrificed. Subsequently, serum calcium fell to very low levels and large doses of calcium and A.T.10 were needed for relief and prevention of tetany.

Six months afterwards he had gained about 20 lb. in weight, his strength and cheerfulness were returning, his serum calcium was within normal limits, and his bones were recalcifying (*Figs.* 277–279). His only complaint at this stage was of persistent hoarseness.

PATHOLOGY.—The first specimen was a homogeneous cellular tumour, 3 cm. in diameter, pinkish-grey in colour, and with a thin capsule.

It was composed of sheets of polyhedral cells, for the most part with diffuse eosinophilic granular cytoplasm,

and clearly defined cell membranes. Some cells were vesicular. Supporting tissue was scanty and consisted chiefly of large numbers of thin-walled blood-vessels with tumour cells arranged radially around them.

The nuclei showed variation in size, shape, and staining, but mitoses were not seen. Some were small, round, and dark, the majority oval and dark, finely stippled with chromatin. Other nuclei were larger, and their chromatin was collected in coarser aggregates, giving them a vesicular

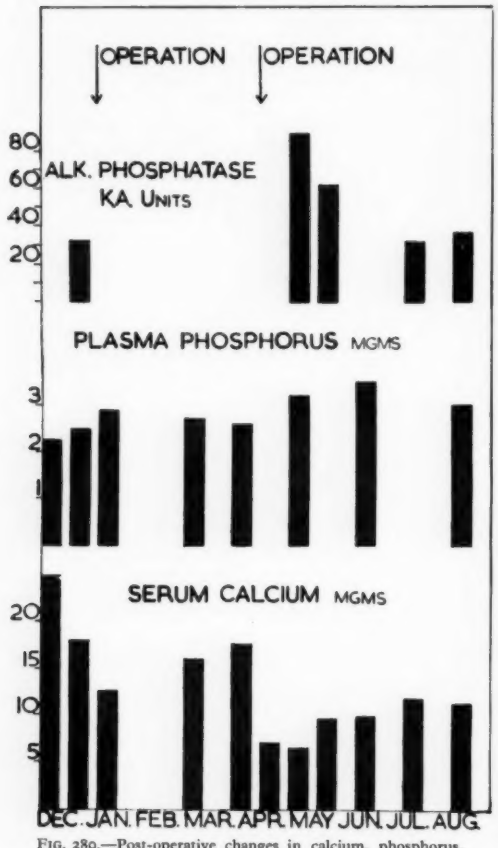


FIG. 280.—Post-operative changes in calcium, phosphorus, and phosphatase levels.

appearance. The nuclei of the cells around the blood-vessels, and in one or two other areas, were spindle shaped (*Figs.* 281, 282).

The second tumour measured 4 × 3 × 3 cm. Its substance was firm and shiny white, here and there tinted with pink. Its substance was divided by septa from the thick fibrous capsule. The centre of the tumour was sharply demarcated by a fibrous tissue shell and contained areas of hæmorrhage and calcification (*Fig.* 283).

In appearance and arrangement its cells closely resembled those of the first tumour; they were likewise well supplied with blood-vessels (*Fig.* 284). Three important differences were noted. Its capsule was thick and fibrous, and wide fibrous tissue septa ran through its substance; the capsule itself was distended by nests of tumour cells, and these were also present in blood-vessels along its margin (*Fig.* 285); mitotic figures were present in moderate numbers in the tumour cells (*Fig.* 286). In one place the tumour was adherent to the thyroid gland and its cells invaded the substance of the gland (*Fig.* 287); in another there was a large collection of tumour cells apparently lying free within the lumen of a thrombosed

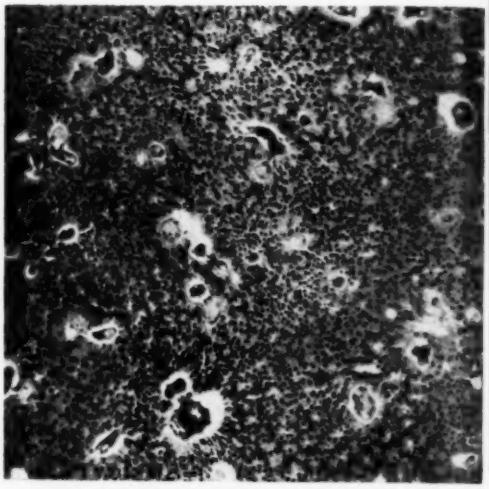


FIG. 281.—Photomicrograph of section of secondary nodule; the tumour is very vascular and the radial arrangement of cells around the vessels is clearly seen. (× 50.)

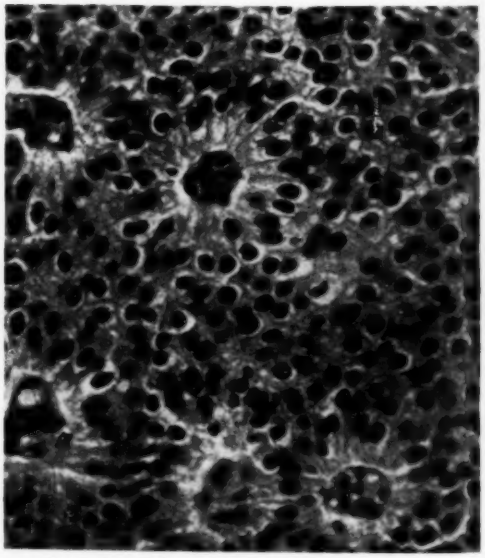


FIG. 282.—Photomicrograph of section of secondary nodule: it consists of eosinophilic cells with large dark nuclei and distinct borders. (× 200.)

vein (*Fig.* 288). There was a normal parathyroid gland lying beside the tumour (*Fig.* 289).

The patient's improvement was maintained for almost 18 months. Since then he has noted mild symptoms: malaise, headache, and constipation, and his serum

FIG. 283.—Photograph of cross-section of primary tumour (actual size). Its substance is white and firm, and shows hæmorrhage and calcification in one area. There is a thick fibrous capsule.

calcium was found to be 12 mg. per 100 ml., phosphorus 2·7 mg., and phosphatase 12 K.A. units. No bony changes are present in the current radiographs. In view of the known tendency of these lesions to recur, even after some years of apparent cure, the patient's eventual prognosis should be regarded with caution.

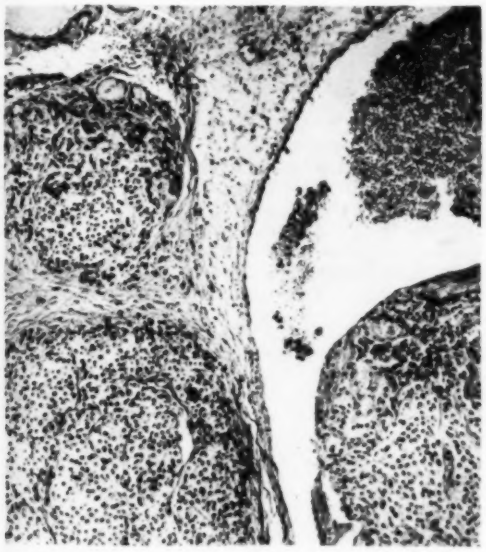


FIG. 285.—Photomicrograph of section of the primary tumour showing a tumour mass within a thin-walled vein. A broad band of fibrous tissue separates two adjoining tumour lobules. (× 50.)

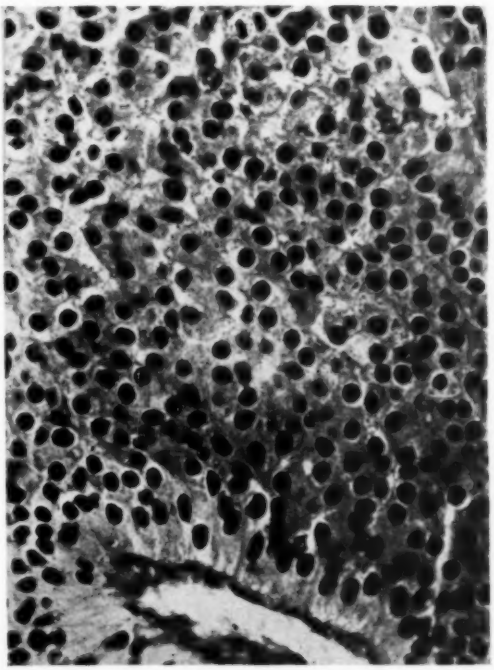


FIG. 284.—Photomicrograph of section of the primary tumour. It is composed of large eosinophilic cells with round or oval hyperchromatic nuclei. The cells are arranged radially around a blood-vessel; at the opposite end of the section is a mitotic figure. (× 200.)

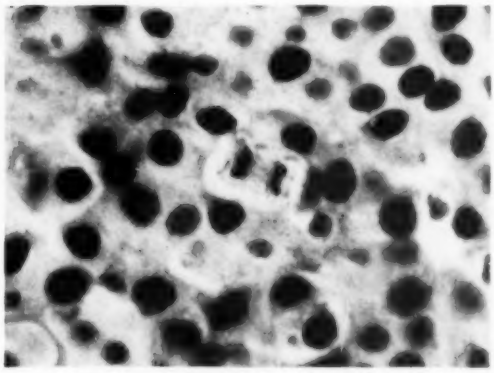


FIG. 286.—Photomicrograph of the primary tumour, showing a cell with a mitosis. (× 500.)

DISCUSSION

The earliest reports of carcinoma of the parathyroid were of non-functioning tumours (Norris, 1948). In other instances (Alexander, Pemberton, Kepler, and Broders, 1944) functioning adenomas were considered, on the basis of histological appearances, to be low-grade adenocarcinomas, a conclusion unsupported by their subsequent behaviour. Both of these interpretations are open to considerable doubt, and it would seem that the diagnosis requires the combination of a hyperfunctioning tumour with local invasion or lymphatic or visceral metastases (King and Wood, 1950; Black, 1954).

Some 24 cases have been collected from the literature which are regarded as satisfying these criteria of invasion or metastasis of a hyperfunctioning

growth. Most of these have been reviewed previously (O'Donovan, Meade, and McGrath, 1951 ; Black and Haynes, 1951 ; Black, 1954). Naturally, interpretations of an individual case differ, and this is particularly so when recurrence

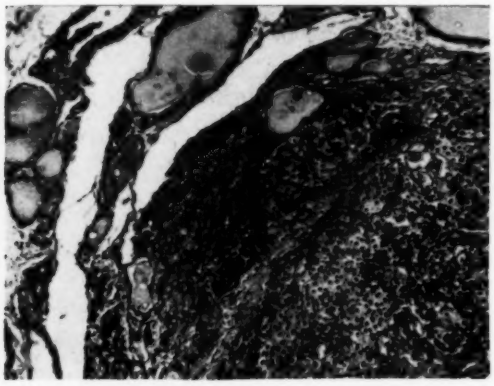


FIG. 287.—Photomicrograph showing parathyroid cells of the primary tumour invading thyroid gland. (× 50.)

FIG. 289.—Photomicrograph showing a normal parathyroid gland lying alongside the primary tumour. (× 5.)

follows operation. Two such cases (Burk, 1947; de Wesselow and de Wardener, 1949) have been included here. Burk implanted a portion of the tumour in an attempt to prevent severe post-operative tetany. Recurrence took place at the site both of the implant and of the original tumour. At the time this was recommended surgical practice and was rarely, if ever, followed by [illegible]ive recurrence (Castleman, 1952). In the other patient a recurrence eventually appeared in the opposite side of the neck.

When this group of patients is compared with a group of patients with parathyroid adenoma (Norris, 1947), only minor differences are observed, and these,

FIG. 288.—Photomicrograph of the primary tumour; tumour masses are present within partially thrombosed vein. (× 5.)

though by no means conclusive, may suggest the possibility of carcinoma (*Table II*).

The incidence is about 3 per cent of adenomas (Castleman, 1952); the ages of the patients range between 16 and 58 years, and the duration of the

Table II.—FEATURES OF PARATHYROID CARCINOMA

Clinical	
	Commoner in males
	Palpable nodule
	Evidence of hyperparathyroidism
	At operation, an adherent tumour or multiple nodules
Pathological	
	Thick fibrous capsule and trabeculæ
	Cords, or masses of polyhedral cells
	Mitoses
	Invasion of surrounding tissues, capsules of veins
	Lymphatic or visceral metastases

disease between 1 and 15 years. The greatest interval between the first operation and recurrence was 5 years, and the shortest 2 months.

Sixty per cent of these patients were males, as opposed to a 70 per cent incidence of adenoma in females. In 60 per cent a nodule could be felt in the neck corresponding to a 10 per cent incidence in patients with adenoma.

The clinical features are those of hyperparathyroidism. The incidence of skeletal and renal lesions shows no significant difference from that in adenoma, and nearly all the recognized complications of parathyroid hyperfunction occurred in these patients. The prognosis, however, is very much

worse; 20 of these patients are known to have died of the disease.

At operation the tumour is often adherent to neighbouring structures; 13 cases are so described. In only one instance was the tumour freely mobile (Meyer, Rosi, and Ragins, 1939). At autopsy 3 years later visceral metastases were found, indicating that this feature is not a reliable guide to the behaviour of the lesion. In 5 patients there were multiple tumour nodules at the first operation—an incidence three times greater than in patients with adenoma (Castleman, 1952).

Although the microscopic appearances of the two lesions differ in several respects, these differences are not sufficiently consistent or striking to provide an easy means of diagnosis. Indeed, it is the rule for metastases to be well differentiated, and for retrospect examination to reveal none but the slightest indications of malignancy in the original tumour. The picture is usually of cords or sheets of eosinophilic granular polyhedral cells, with clearly defined cell borders. Often many cells are vesicular and their boundaries even more sharply accentuated. The capsule is usually thick and fibrous, and broad trabeculæ pass from it into the substance of the tumour. Thin-walled blood-vessels are plentiful, and about these the cells are radially arranged. Here, and in other situations, groups of cells are cylindrical or spindle-shaped. The cells and their nuclei tend to be larger than those of an adenoma. The nuclei, though pleomorphic, are for the most part oval, and giant forms are rare. They contain abundant chromatin, as a fine stippling or in coarser clumps, and an eccentric nucleolus.

Three features—mitosis, tumour cells within the capsule and in veins—prominent in carcinoma are said to occur also in adenoma (Norris, 1947; Black and Ackerman, 1950). Some dissent from this opinion and one worker (Castleman, 1952), from an experience of 100 patients with hyperparathyroidism (including 8 with carcinoma), states that mitoses were present in the patients with carcinoma and absent from those with adenoma. In three of the reports reviewed here mitoses are stated to have been absent.

It is probably impossible to resolve this point, but not unreasonable to conclude that the presence of mitoses and the invasion of veins and capsule to a significant degree should suggest the diagnosis of carcinoma; this is to be confirmed by the criteria set out above: local invasion and lymphatic or visceral metastases.

The knowledge that this type of tumour may produce hyperparathyroidism is of more than theoretical importance, and should always influence the surgeon in his management of the patient.

SUMMARY

A patient with carcinoma of the parathyroid has been described.

Twenty-four such reports have been collected and reviewed. The criteria for provisional and final diagnosis are discussed, and it is pointed out that, though they have been regarded as excessively rare, the gradually increasing number of recorded cases indicates that these are of importance in surgical practice.

Acknowledgement.—This patient was admitted under the care of Dr. G. A. Penington, and I am indebted to him for permission to publish details of the case.

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ŒSOPHAGEAL STRICTURE FOLLOWING INTUBATION IN A CASE OF HIATUS HERNIA

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THIS is the description of a case in which cholecystectomy and drainage of the bile-duct were properly undertaken for gall-stones causing colic and obstructive jaundice and associated with cholecystitis. There was also, however, a hiatal hernia which had produced, in all probability, some of the dyspeptic symptoms of epigastric pain and regurgitation and caused some degree of œsophageal mucosal damage. This hernia had not been demonstrated radiologically or diagnosed before operation. After operation severe and persistent distension and vomiting necessitated the use of an indwelling red rubber Ryle's tube, for fifteen days. It is postulated that the hiatal hernia and the œsophagitis accompanying it, the persistent vomiting and the prolonged intubation it necessitated, and the plasticizer in the red rubber, all contributed in the causation of a severe and impassable stenosis for which operative relief was undertaken, with a fatal outcome.

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CASE REPORT

The patient was a stout hypertensive woman aged 50 years, who had had irregular attacks of epigastric pain with flatulence and sometimes vomiting during the past 16 years. Four months before admission a more serious attack of pain than usual was followed by severe vomiting, and later by jaundice and the passage of dark urine. In September, 1954, cholecystectomy and drainage of the common bile-duct were performed. Gall-stones were found in an inflamed gall-bladder and in the common bile-duct.

After operation the patient had persistent paralytic ileus. A Ryle's tube was used in treatment and was left in for 15 days. It was a red rubber tube of the usual type, and seemed to cause her more soreness and discomfort than usual. She appeared to have made a full recovery when, two weeks after the removal of the tube, dysphagia appeared. Five weeks later she could not swallow enough fluid to live on and gastrostomy had to be performed.

Barium swallow (*Fig.* 290) at this time showed a smoothly tapering stricture of the lower end of the œsophagus. Œsophagoscopy confirmed the stricture at 24 cm., through which a dilator could not be passed. Above the impasse for a distance of 1 cm. there was a

FIG. 290.—Barium examination of the œsophagus showing a smoothly tapered stricture through which only a minute trickle of barium passed.

FIG. 291.—Barium introduced into the stomach through the gastrostomy tube shows a well-developed hiatal hernia. This was easily reducible.

sloughing of the œsophageal walls. Above this again there was a rapid change to mucosa which was only mildly inflamed. Barium introduced by means of the gastrostomy outlined a reducible hiatus hernia (*Fig.* 291). Further attempts at œsophageal dilatation over a period of 4 months were unsuccessful in re-establishing a lumen and so thoracotomy was undertaken to reconstruct the lumen.

At operation a dense induration 5 cm. long was felt at the site indicated in the radiograph. The superficial appearance was almost normal and at first sight there was little on the surface to indicate the gross changes found later within the lumen. There was no appreciable peri-œsophagitis. The hiatal hernia was confirmed. The stricture was explored by a longitudinal incision and no satisfactory lumen could be found in the affected part. The mucosa seemed to have been completely destroyed. A polythene tube was passed from the mouth across this part into the stomach and the almost unaffected muscle sewn over the top.

Following operation there was severe hypotension, probably of cardiac origin, which failed to respond to noradrenaline. Death occurred in circulatory failure on the fourth post-operative day.

DISCUSSION

About 30 cases of œsophageal stricture following intubation have been reported in the literature. Gastric intubation is a common hospital procedure. While it is unusual to retain the tube for 15 days, its retention for so long a period is not rare in a large general hospital, yet a subsequent stricture from this cause has not previously been recognized in this hospital.

The development of a stricture in this case demonstrates perhaps the synergism of several aetiological factors.

1. A previous œsophagitis associated with the hiatal hernia which, because of its size and easy reducibility, was undoubtedly there before operation and not caused by recent œsophageal shortening.

2. Trauma of the indwelling tube, for it is known that any indwelling rubber tube will produce epithelial irritation and possibly superficial ulceration. This damage has been repeatedly observed, for example, in the urethra and the pharynx and œsophagus.

3. Red rubber, or the plasticizer it contains, seems to be more irritant than latex or polythene. It produces a higher incidence of intravenous thrombosis and a higher incidence of urethritis.

4. The role of persistent post-operative vomiting, such as this patient had, is considered important. In 60 cases of benign stricture of the œsophagus, Benedict and Sweet (1948) stress the role of gastric acid secretion in the aetiology of this condition.

The lesson to be learnt from this unfortunate case is that in the treatment of post-operative vomiting in patients likely to have hiatal hernia the prolonged use of indwelling œsophageal tubes may carry risks, and the risk may be increased if the tube is made of red rubber.

SUMMARY

A case of œsophageal stricture is described, following the prolonged use of a red rubber Ryle's tube in the treatment of distension and vomiting after biliary surgery, in a patient who also had an undiagnosed hiatal hernia.

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A CASE OF AMYLOID GOITRE AND INFERIOR VENA CAVA THROMBOSIS

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WHILE Henke and Lubarsch (1926) observed varying degrees of amyloid infiltration in 90 per cent of a small series of patients, and Pasma and Hadders (1952) commented that the infiltration was not unknown in cases of generalized amyloidosis, true thyroid enlargement produced by this condition is rare. Only 45 case reports were found in an extensive survey of the literature: in a review by Walker (1942) 37 cases; Means (1947) and Case Reports of the Massachusetts General Hospital (1947) 2 cases each; Covarrubis and Calderon (1943), Jacmet (1951), Pasma and Hadders (1952), and Brandenburg (1954), 1 case each.

CASE REPORT

A 41-year-old male, on admission to hospital (November 28, 1956), complained of 6 months' progressive dyspnœa and of 10 weeks' mild increasing dysphagia. Over the same period a bilateral thyroid swelling of 3 years' standing had rapidly expanded. He also complained of a moderately productive cough and some hoarseness of voice. Ankle œdema of slight degree would develop after several hours' activity. There was no definite evidence of hypothyroidism, Addison's disease, or of alimentary or urinary symptoms.

During the preceding 10 years bilateral apical pulmonary tuberculosis had been a recurrent problem. For 6 years para-amino salicylic acid had been prescribed intermittently in routine doses. Five years previously a severe tuberculous meningitis responded well, but only after vigorous therapy for 16 months. The meningitic episode developed while the patient was in hospital being treated for progressive generalized tuberculosis. At this time (August, 1951), the urine repeatedly contained 400–700 mg. per cent protein, but there were no casts or other abnormalities in several samples. The total plasma proteins were 5·6 g. per cent; the plasma albumin was 2·8 g. per cent. Renal amyloidosis was suspected but not proved by these limited investigations.

On April 30, 1952, 8 months after the first observation of the above abnormalities, and 2 weeks after the rather difficult induction of a pneumoperitoneum, the patient complained of a non-tender swelling of the whole of the right leg which showed a generalized slight pitting œdema, and the superficial veins over the right thigh and the right side of the lower abdominal wall became very prominent.

On May 29, 1952 the left leg displayed a swelling which rapidly increased over the next few days, and subsequently the lower abdominal veins on the left side, and the veins on the left thigh, became very distended. A month later the bilateral swelling had largely disappeared except for a slight persisting tendency to ankle œdema. The anterior veins had, however, remained very prominent over an area extending from mid-thigh to lower chest. During the initial episode the attending physician (Dr. W. S. Hamilton) diagnosed a thrombosis of the right iliac vein with subsequent involvement of the left iliac vein and finally of the inferior vena cava.

FIG. 292.—Radiograph of neck and upper thoracic limits showing tracheal displacement and compression as well as the goitre, and chronic apical tuberculosis.

FIG. 293.—Photograph of extirpated specimen showing particularly enlarged right lobe.

ON EXAMINATION.—A moderately fit looking male with a temperature of 98·8° F. There was no evidence of hypothyroidism, and the tongue, gums, lymph-nodes, and upper chest wall veins were normal. The thyroid gland was generally enlarged, with a particularly large right lobe which displaced the trachea far to the left (*Fig.* 292). In this area a mild stridor was audible through a stethoscope.

The other abnormalities were very prominent veins anteriorly between upper thigh and lower chest associated with slight bilateral pitting ankle œdema. Both pulmonary apices displayed typical signs of a moderately active chronic pulmonary tuberculosis. The upper surface of most of the left vocal cord and the left arytenoid showed typical tuberculous ulceration, but both cords moved normally. The heart beat vigorously at 80 pulses per minute, and the blood-pressure was 135/80. The liver and spleen were not palpable.

AT OPERATION.—Partial thyroidectomy was performed on December 7, 1956 (Mr. Moloney), before the true diagnosis was known. At operation the gland was normally mobile and encapsulated with no retrosternal prolongation. The cut surface had a very firm gelatinous consistency which was remarked on as an unusual appearance which might have meant neoplasia. In anticipation of hæmostatic problems the resection was slightly limited, and, in fact, considerable difficulty was experienced because of the shreddy nature of the tissue over the line of excision. Sutures biting deeply into the adjacent capsule were finally successful in stopping the bleeding.

Investigations were carried out in the pre- and post-operative periods. Two months before operation (in contrast to the earlier massive albuminuria) the urine on two occasions contained less than 10 mg. per cent of protein, and no casts. The blood-cholesterol, plasma bilirubin, and liver flocculation tests were normal. I^{131} uptake was virtually nil, and the total plasma proteins and plasma albumin were 7·3 and 1·7 g. per cent respectively. A high-protein diet was prescribed.

The sputum contained numerous acid-fast bacilli. Radiographs immediately before operation displayed a large thyroid causing marked compression and displacement of the trachea (*Fig.* 292), bilateral apical tuberculosis, and a normal sized heart. The B.M.R. was not estimated.

Post-operatively further tests were performed. After 12 hours' total deprivation of water, the urine specific gravity was 1·020. It contained more than 1000 mg. per cent protein, but definite hyaline casts only occasionally, even in 3 fresh specimens. The urea content was 0·4 g. per cent; the chloride 2·5 g. per cent.

The blood was extensively analysed: Hb, 94 per cent; W.B.C., 14,000; platelets, 348,000; blood-urea, 40 mg. per cent; total plasma proteins, 5·3 g. per cent; plasma albumin, 2·5 g. per cent. The plasma chloride, serum sodium, and potassium values were normal.

Twenty-five per cent of an intravenous injection of 17·5 c.c. of 1 per cent indigo carmine was absorbed from the blood after one hour.

Gingival, liver, and renal biopsies were not performed. The electrocardiogram revealed mild right axis deviation. There was no evidence of myxœdema.

The post-operative course was uneventful. Dyspnœa was mostly relieved, and dysphagia entirely, but hoarseness was unchanged.

PATHOLOGY.—The specimen weighing 230 g. (*Fig.* 293) consisted of the isthmus and part of both lobes of a

diffusely enlarged thyroid (right lobe, 13 × 8 × 5 cm.; left lobe, 11 × 6 × 3·5 cm.). Prominent veins were visible under the smooth external surface. The largely homogenous cut surface was firm, pale yellowish-brown, and traversed by a few fine fibrous bands. The iodine test for amyloid gave a diffuse mahogany brown colour.

Microscopically the appearances (*Figs.* 294, 295) were those of amyloidosis. The thyroid acini were widely

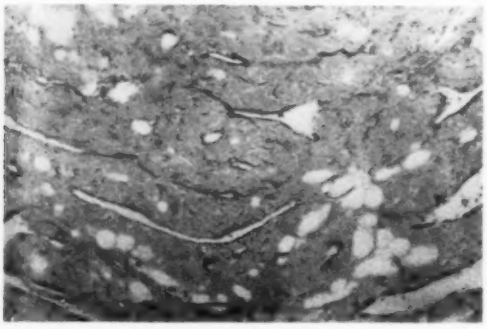

FIG. 294.—Slide displaying thyroid acini widely separated by diffuse interstitial deposits of eosinophilic material. H. and E.

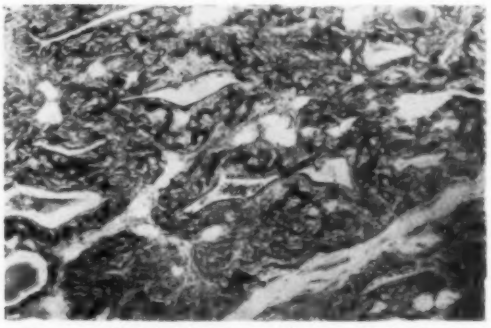

FIG. 295.—Methyl violet stain revealing areas of fibrosis and widely separated acini.

separated by diffuse interstitial deposits of eosinophilic material which gave positive staining reactions for amyloid with the Van Gieson, congo red, and methyl violet techniques. The acini were lined by small cuboidal cells and frequently contained no colloid. Many acini were small or reduced to narrow clefts owing to compression by the amyloid, but scattered enlarged acini were present. While most of the amyloid was homogenous, in places a faint lamination was visible. Fat cells often surrounded by amyloid were plentiful. There were a few areas of fibrosis in the interstitial tissues (*Fig.* 295).

SPECIAL ASPECTS OF PATHOLOGY

Primary amyloidosis is exceedingly rare. Most of the cases already mentioned developed secondarily to tuberculosis (very often apical pulmonary). A very few developed in relationship to neoplasia, bronchiectasis, rheumatoid arthritis, or multiple myelomatosis (Walker, 1942).

While prolonged courses of P.A.S. can be goitrogenic (Davies and Galbraith, 1953), the histological picture here excluded this pathology.

The laryngeal ulcer and thrombosis of the inferior vena cava merit attention. While the laryngeal ulcer was classically tuberculous, so-called amyloid tumours of the vocal cords do occur (Brown-Kelly and Craik, 1952). Renal vein (bilateral and unilateral) and inferior cava thromboses have been described as a not infrequent complication of generalized amyloidosis, as cited by Siegmund (1935) 3 cases; Opsahl (1936) and O'Beirn (1953) 2 cases each; Rosenberg and Munter (1924), Zadeck (1929), Schawecker (1930), Herzog (1913), Schroeder (1926), Campannini (1942), Flynn (1945), and Case Reports of Massachusetts General Hospital (1956), 1 case each. The risk is particularly marked after operative intervention.

DIAGNOSIS

Such a rare condition may easily be omitted from the differential diagnosis, and clinically the most common error is to confuse it with malignancy or a simple diffuse goitre.

However, once the pathology is suspected on the basis of the history and clinical examination diagnosis is less difficult. Typically, thyroid function is not disturbed. Hypothyroidism is uncommon (Walker, 1942), and only 2 cases of associated thyrotoxicosis have been recorded (Pasma and Hadders, 1952; Walker, 1942). Histologically, Pasma and Hadders's case displayed marked amyloid infiltration sufficient to cause considerable enlargement, as well as the typical hyperplasia of hyperactive thyroid tissue. Thyroid function can be estimated by radio-active iodine uptake, B.M.R., and electrocardiography. Roentgenological examination of the thyroid area will display impingement on the trachea as well as retrosternal prolongations. The renal state can be assessed by repeated searching in fresh urine for amyloid casts, quantitative albumin, and Bence Jones protein (in case of myelomatosis), and by concentration and dilution tests. The urinary-urea and chloride as well as the blood-urea and blood-pressure should be estimated. A chest radiograph will display pulmonary lesions as well as the heart's configuration. An estimation of blood-electrolytes may bring to light an associated hypo-adrenalism.

As in this case the congo red test is often unreliable. In defining strict diagnostic criteria, Selikoff (1947) stated that over 90 per cent of the standard intravenous dose should be absorbed within the first hour, and that in the case of a positive result the test should be repeated in order to exclude those normal people who (during the first test only) may absorb from the blood-stream as much as 90 per cent of the dye. False negatives occur particularly in the presence of small amyloid deposits.

Biopsies of the liver, kidneys, and gums, and of the thyroid itself, will further clarify the picture.

DISCUSSION

While expanding resources against predisposing conditions have greatly diminished the incidence of amyloidosis, this rare form might occasionally still be considered. In particular its management is quite different from the neoplastic state with which it is so easily confused. At operation in this case, for example, the diffusely friable gland suggested a

malignancy, and the immediate problem was to decide whether to relieve the pressure effects only or to perform a much more radical excision. A pre-operative diagnosis of amyloidosis would have settled this problem, and at the same time given a warning of possible difficulties with bleeding during the operation and of the increased risk of major vein thromboses.

While Joll (1951), largely because he feared post-operative myxœdema, advised against operation, some patients rather urgently seek relief from pressure effects and thus force the surgeon to operate in spite of the possibility of finding an amyloid goitre. In any case post-operative myxœdema can be easily controlled.

Since the diagnosis is usually made retrospectively from microscopical examination of surgical excised tissues, the numerous investigations described above are mostly directed either towards a valuable assessment of the patient's general state or towards academic study. Renal function should receive particular attention.

It is logical to expect that after the resection of a large mass of amyloid tissue the congo red test may be particularly misleading.

In many cases the more complicated, but occasionally dangerous, measures of renal and liver biopsy may be hard to justify. One must appreciate that the pathology is rarely confined to the thyroid. The urinary and plasma proteins alone may often be very suggestive of renal amyloidosis, as exemplified by this case.

Once the diagnosis is established, the primary condition (e.g., tuberculosis) must be vigorously treated.

SUMMARY

1. A large amyloid goitre led to marked pressure symptoms in a patient who had also suffered from chronic pulmonary tuberculosis and thrombosis of the inferior vena cava.

2. Amyloid goitre is rare, but in generalized amyloidosis a mild thyroid infiltration is very common.

3. The post-operative congo red test was unreliable in this case, as it has been in many others.

4. Thrombosis in the inferior cava and renal veins is associated with generalized amyloidosis and is a particular risk post-operatively.

I wish to thank Mr. G. E. Moloney and Dr. W. S. Hamilton for their permission to publish this case, and for all their generous advice and assistance in preparing this article. I am also indebted to Dr. D. Richards, Assistant Pathologist, Radcliffe Infirmary, Oxford, for the photomicrographs and histological report.

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EXPERIMENTAL SURGERY

THE CONTROLLING INFLUENCE OF THE PITUITARY ON THE GROWTH OF THE NORMAL BREAST

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INTRODUCTION

THE experiments to be described in this paper were carried out in an attempt to define the nature and origin of the mammogenic agent present in the urine (Scowen and Hadfield, 1955; Hadfield and Young, 1956 a, b), and in the blood-serum of healthy women (Hadfield and Young, 1958).

Using hypophysectomized immature male mice of the A2G strain it has been repeatedly demonstrated that the mammogenic triad of hormones—prolactin, œstrogen, and progesterone—induces an unequivocal growth response in the rudimentary and partially atrophic mammary glands of the mice. If human urine or blood-serum be substituted for the pituitary component of this triad, a similar mammary growth response can be induced in the hypophysectomized mouse.

Substitution experiments of this kind suggest that the agent present in human serum and urine is produced by the anterior pituitary and may be prolactin. During the last two years, research work in several countries on the physiological action of extracts prepared from human anterior pituitary glands has opened up a new and realistic experimental field. It has, for instance, been shown that the mammary glands of *intact* weanling male mice are remarkably sensitive to the mammogenic hormone or hormones contained in the extracts of the human pituitary (Donath, Hadfield, and Scowen, 1958). Experiments are now reported in which crude extracts of human anterior pituitary glands were injected into totally hypophysectomized weanling male mice.

Lyons and his co-workers (Lyons, 1958; Lyons, Li, and Johnson, 1957) have demonstrated that pituitary growth hormone (somatotrophin) plays a part in the initial phase of mammogenesis which leads to the formation of a mammary duct system in the hypophysectomized rat. An account of experiments designed to study this important relationship in the totally hypophysectomized A2G weanling male mouse is included in this paper.

Apart from the intact animals used as controls, we have used hypophysectomized mice in all the experiments reported in this paper, and the completeness of the hypophysectomy operation has been confirmed by cutting serial sections of the pituitary fossæ of all test animals.

MATERIALS AND METHODS

Animals.—Strong A2G weanling male mice weaned at the age of 21 days (body-weight, 7·5–9·5 g.) and hypophysectomized when 22–24 days old, were used in all experiments. (The animals were bred in our own laboratories; other colonies are being maintained under genetic control in other centres.*)

Hormone Controls.—During the period of the experiment the mammæ of batches of intact weanlings were examined to verify that the animals of the colony were not being subjected to dietetic or other extraneous mammary stimulation. When combinations of ovarian and pituitary hormones were given, each component of the combination was injected into separate groups of mice.

Injection Programme.—Injections were started several days after operation when the pre-operative body-weight was restored; 2 injections a day were given for 5 days in all experiments.

Hypophysectomy Control.—Each pituitary fossa yielded about 250 serial sections. When the sections have revealed easily recognizable anterior pituitary tissue the animal has been rejected. When minute cellular fragments of uncertain origin have been found the animal has been rejected if the cytoplasm of an appreciable number of the cells of the fragment was clearly eosinophilic.

Preparation of Mammæ.—The skins, fixed in Bouin's solution, were dehydrated, 'defatted' in xylol to facilitate dissection from the pelt, stained in Grenacher's alum-carmine, and the stained glands dissected out and mounted. Six mammary glands were usually obtained from each mouse.

Estimation of Mammary Growth Response.—This was determined by estimating the mean number of large, deeply-staining end-bulbs or 'clubs' per gland (*Fig.* 296). As the free ends of the ducts may be slightly swollen in untreated controls, a swollen duct end was not counted as a 'club' unless its short diameter was greater than twice that of its parent duct. The mammary glands of groups of normal intact untreated weanling males, totalling 164 animals, were examined at intervals over the period of the experiments here reported. The average number of large clubs per mammary gland in these untreated animals was 0·3 (*Table I*).

Table I.—CLUBS PER GLAND IN NORMAL INTACT UNTREATED CONTROL MICE (A2G STRAIN) DURING THE PERIOD OF THE EXPERIMENTS

No. of Mice	*Total Glands*	*Total Clubs*	*Clubs per Gland*
164	858	273	0·3

* Laboratory Animals Centre, Medical Research Council, Woodmansterne Road, Carshalton, Surrey; Imperial Cancer Research Fund Laboratories, Mill Hill, London.

In reacting glands, the number of clubs per gland when divided by the number of clubs per gland in intact untreated controls is regarded as a measure of the experimentally-induced growth response. The results of an experiment in which 10 intact animals were given œstrone and progesterone for 5 days are shown in *Table II*. In these treated animals the number of clubs per gland was 18, and the quotient $\frac{18}{0.3}$ gives a growth response of 60.

Table II.—Estimation of Mammary Growth Response induced in Intact Weanlings by Ovarian Hormones

No. of Mice	*Total Glands*	*Total Clubs*	*Clubs per Gland*	*Mammary Response*
10	59	1060	18	60

Group II. Human Anterior Pituitary Extract.—The glands used were from pre-menopausal women who died from trauma, suicide, or diseases which were probably unaccompanied by any material abnormality of pituitary function.

The glands, removed at post mortem, were put through several changes of absolute acetone. The glandular capsules and posterior lobes were removed. The anterior lobes were then freeze-dried, finely powdered, and stored in dry nitrogen over phosphorus pentoxide.

Two groups each of 20 hypophysectomized mice were given the weighed amount of powdered crude extract corresponding to one-tenth of a single anterior lobe, vigorously shaken in the requisite quantity of distilled water and injected as a suspension. One group of 20 animals received the amount corresponding to half a single gland. The hypophysectomized mice tolerated the extracts at this high concentration remarkably well. The results of the experiments are shown in *Table IV*.

Table III.—Mammary and Somatic Growth in Hypophysectomized and Untreated Weanling Mice

Total Mice	Evidence of Mammary Growth	Mean + or − Body-weight per Mouse per Day in g.	Standard Error of Difference	t	Probability	Result
21	Nil. Glands atrophic	−0·070	±0·0213	3·3	<0·01	Significant loss

Table IV.—Mammary and Somatic Growth Responses induced in Hypophysectomized Weanlings given Crude Extracts of Human Anterior Pituitaries

Total Mice	Given Human A.P. Extract	Mammary Growth Response	Mean + or − Body-weight per Mouse per Day in g.	Standard Error of Difference	t	Probability	Result
20	$\frac{1}{10}$ gland	7·0	+0·2105	±0·0480	4·4	<0·001	Significant gain
20	$\frac{1}{10}$ gland + œstrone + progesterone	59·0	+0·2575	±0·0185	13·95	<0·001	Significant gain
20	$\frac{1}{2}$ gland + œstrone + progesterone	63·0	+0·2378	±0·012	19·88	<0·001	Significant gain

RESULTS

The animals were divided into the following four groups:—

Group I. Control group—hypophysectomized: untreated.

Group II. Human anterior pituitary extract group.

Group III. Prolactin group.

Group IV. Growth hormone group.

The individual animals in all experiments were weighed daily and the mean gain or loss of weight per mouse per day between hypophysectomy and death was calculated. Several batches of normal intact untreated weanling males of the same age were weighed during the period of the experiments. They showed a normal mean increase of 0·51 g. per day per mouse ($P<0·001$)

Group I. Controls—Hypophysectomized: Untreated.—The results obtained are shown in *Table III*.

These results suggest that the hypophysectomized weanling male mouse reacts specifically and satisfactorily to the hormones of the human anterior pituitary. As was anticipated, the doses given were needlessly large, the mammary and somatic growth responses suggesting that both dose levels had induced maximum responses. The presence of growth hormone was indicated by a highly significant increase in body-weight and this was produced in the presence or absence of ovarian steroid hormones. Prolific mammary growth responses were induced by human pituitary extracts in conjunction with ovarian steroids. A comparatively weak mammary response was produced by injection of the extract alone. This is regarded as indicating the presence of gonadotrophin in the extract, this hormone being responsible

for stimulating the gonads of the mouse and the production of steroid hormones.

Group III. Prolactin*.—Five batches of animals were used. In the first, prolactin alone at a high total level of 50 I.U. (=2·5 g.) was given over a period of 5 days. In the remaining 4 groups, contamination of our sample of prolactin by growth hormone—which we know to be between 1 and 0·1 per cent., i.e., 2·5 mg. of this prolactin contains a maximum of 0·025 mg. of growth hormone. Reference to the results obtained with growth hormone (*Table VI*) indicates that this amount of contaminating

Table V.—Mammary and Somatic Growth Responses induced in Hypophysectomized Weanlings given Prolactin*

Total Mice	Given Prolactin	Mammary Growth Response	Mean + or − Body-weight per Mouse per Day in g.	Standard Error of Difference	t	Probability	Result
18	2·5 mg.	Nil	+0·0739	±0·0134	7·0	<0·001	Significant gain
10	0·01 mg. + œstrone + progesterone	13	−0·0420	±0·022	1·59	>0·1	No significant difference
20	0·045 mg. + œstrone + progesterone	18	−0·0840	±0·0157	5·35	<0·001	Significant loss
41	0·225 mg. + œstrone + progesterone	36	+0·0075	±0·0451	0·16	>0·2	No significant difference
5	0·45 mg. + œstrone + progesterone	50	+0·0900	±0·0556	1·62	>0·1	No significant difference

* The prolactin used in this work was a gift from the Endocrinology Study Section, National Institutes of Health, Bethesda, Maryland, U.S.A. It is a highly purified sheep preparation estimated to contain 20 I.U. per mg. Contamination with growth hormone = less than 1 per cent.

Table VI.—Mammary and Somatic Growth Responses induced in Hypophysectomized Weanlings given Growth Hormone*

Total Mice	Given Growth Hormone	Mammary Growth Response	Mean + or − Body-weight per Mouse per Day in g.	Standard Error of Difference	t	Probability	Result
14	1·0 mg.	Nil	+0·2014	±0·0390	5·2	<0·001	Significant gain
20	0·04 mg. + œstrone + progesterone	39·5	+0·1295	±0·0143	9·1	<0·001	Significant gain
20	0·20 mg. + œstrone + progesterone	47·6	+0·2035	±0·0193	10·0	<0·001	Significant gain
5	1·0 mg. + œstrone + progesterone	57·0	+0·2540	±0·0391	6·5	<0·001	Significant gain

* The growth hormone used in these experiments was kindly supplied by Dr. S. J. Folley of the National Institute for Research in Dairying, Shinfield, near Reading, Berkshire.

prolactin at a series of lower dose levels was given with ovarian steroids at a constant total dose of œstrone 1·25γ and progesterone 7·5 mg. over 5 days. The results obtained are shown in *Table V*.

These results again demonstrate in the hypophysectomized weanling mouse that prolactin in the absence of ovarian hormones is unable to induce a mammary response and, as on several previous occasions, we were again able to demonstrate that ovarian steroids in the absence of a pituitary mammogenic factor are equally powerless to do so. The highly significant gain in weight in animals given prolactin alone at a high dose level is in all probability due to growth hormone would be able to produce an increase in body-weight of this order. Prolactin at lower dose levels in synergism with ovarian steroids, although inducing a rapid and significant response in the mammary glands (*Figs.* 297, 299), did not induce any significant increase in body-weight.

Group IV. Growth Hormone.—The plan of these experiments was identical with that in which prolactin was given; the results are shown in *Table V*.

As with prolactin, growth hormone alone in the absence of ovarian hormones failed to induce a mammary response, but in synergism with ovarian steroids the responses were unmistakable (*Figs.* 296,

298). The degree of contamination with prolactin of the growth hormone used was too small to have made any material difference to the mammary growth response. In the sharpest contrast with prolactin, growth hormone at all dose levels, with or without ovarian hormones, induced a significant increase in body-weight.

Our results are briefly summarized in *Table VII*.

Table VII.—Mammary and Somatic Growth Responses to Hormonal Stimulation of Hypophysectomized Weanlings

Injections in Hypophysectomized Mice	Mammary Growth Response	Body-weight
Extracts of human anterior pituitary		
1. Alone	Weak	Significant increase
2. With œstrone + progesterone	Prolific	Significant increase
Growth hormone		
1. Alone	Nil	Significant increase
2. With œstrone + progesterone	Prolific	Significant increase
Prolactin		
1. Alone—at high dose levels	Nil	Significant increase
2. At lower dose levels with œstrone + progesterone	Prolific	Significant loss or no significant gain

DISCUSSION

The stimulation of mammary and somatic growth in hypophysectomized mice by extracts of human pituitary glands shows that the mammary glands of these animals are remarkably responsive to human pituitary hormones. To some extent this sensitivity of the mouse mamma increases the significance of our previous experiments which led us to believe that human urine and serum contain a pituitary mammogen.

The stimulation of somatic growth in the hypophysectomized mouse by human pituitary extracts is a clear indication that such extracts contain growth hormone. As our second series of experiments confirms the observation that growth hormone in synergism with ovarian hormones is mammogenic (Lyons, 1958; Lyons and others, 1957), *it may now be possible to identify a pituitary mammogen in human urine or serum by inducing a significant increase in body-weight in hypophysectomized mice by the injection, with ovarian hormones, of concentrates prepared from human urine or serum.* We would, however, suggest, in view of our repeated failures to reach an adequate degree of concentration of urine or serum by simple methods, that nothing short of an elaborate electrophoretic concentration technique would be successful.

It has already been mentioned that the increase in body-weight induced by prolactin acting at a high dose level in the absence of ovarian hormones was in all probability due to growth hormone which contaminated our sample of prolactin to a maximum of 1 per cent. In other experiments in this group prolactin at much lower dose levels was given with ovarian hormones. None of the animals in this series showed any significant increase in body-weight but at all doses an unequivocal mammary growth response was induced (*Figs.* 297, 299). After calculating the maximum amount of growth hormone contaminating each dose of prolactin given, we concluded that the mammary growth responses obtained could not have been induced by growth hormone. We must therefore conclude, at least in the hypophysectomized A2G weanling mouse, that prolactin at relatively low dose levels in synergism with ovarian hormones stimulates the early stages of mammary growth without inducing an increase in body-weight, whilst growth hormone at approximately the same dose level induces similar or even identical mammary growth responses and a significant increase in body-weight. Our experimental data offer no obvious explanation for these findings.

Lyons deduced from his experiments that the control of the mammary growth exercised by growth hormone in synergism with ovarian hormones is limited to the early phase of mammogenesis which culminates in the production of a duct system. Our results confirm this. They were amplified by histological studies of the mammary glands of hypophysectomized mice in which growth responses had been induced by human urine and serum, prolactin, growth hormone, and human pituitary extract, all of which were given with ovarian hormones over a period of 5 days. In mice with *intact pituitaries and adrenals* it is possible to induce well-defined glandular differentiation over this period by the administration of prolactin, but in all our experiments using totally hypophysectomized animals acinization of the mammary glands was absent or trivial, and even when mammary growth was prolific the glands were still in the initial or mitotic phase of growth which ends in the formation of a mammary duct system (*see Figs.* 297, 299). During this phase, epithelial proliferation at the free ends of the ducts reaches its maximum. It merges into, and is eventually replaced by, the phase of glandular differentiation during which mitotic activity subsides to a comparatively low level and each conspicuous club-shaped mass of young undifferentiated epithelial cells at the free ends of the smaller ducts (*Fig.* 299) is transformed into a compact group of gland tubules.

In hormone-dependent human breast cancer one or probably more mammogenic hormones are responsible, to a varying degree and for an uncertain period of time, for the maintenance of a population of malignant cells whose major and probably only activity is proliferation by mitosis.

We would suggest, therefore, that a study of the hormonal factors controlling the initial mitotic phase

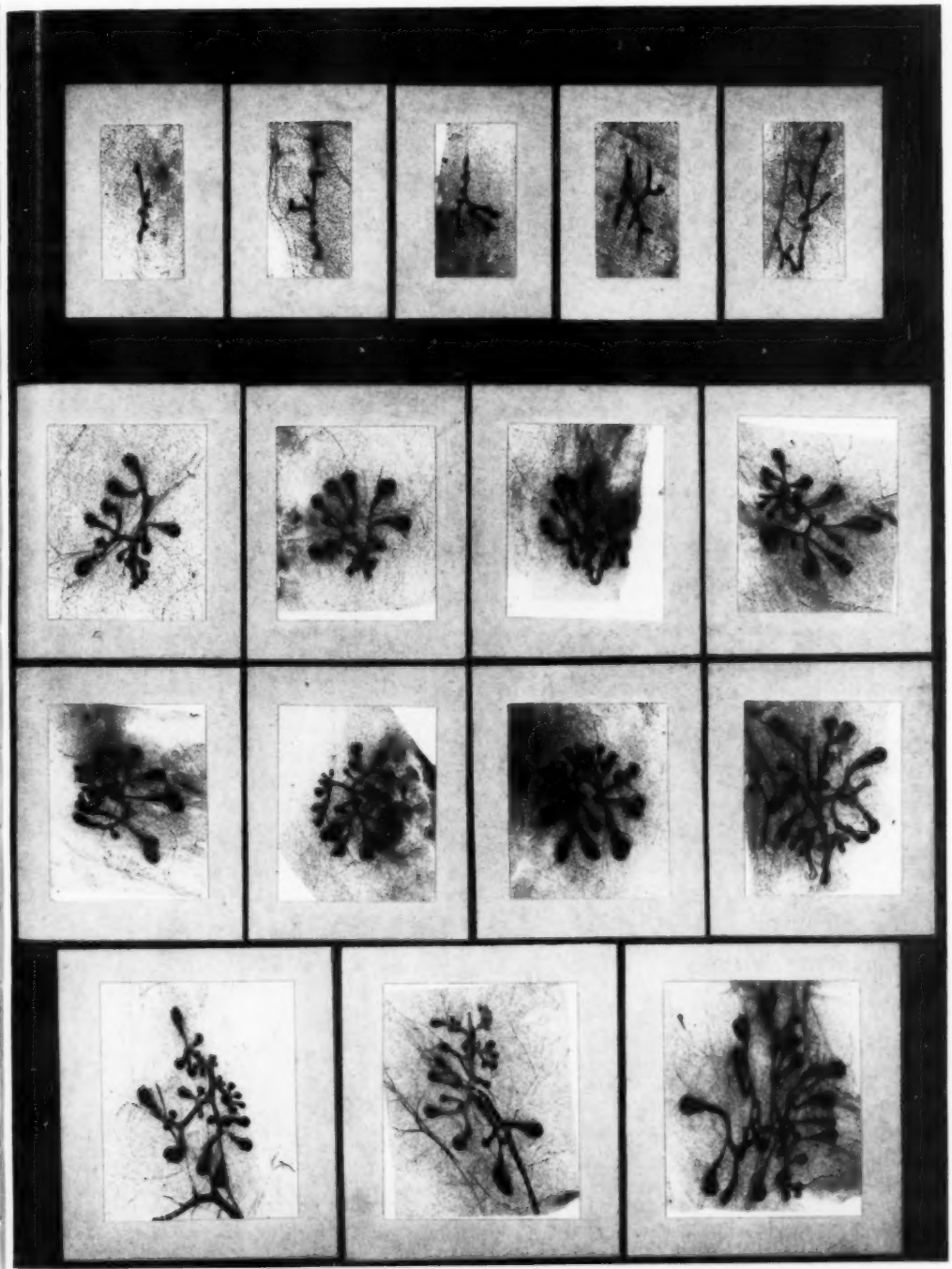

FIG. 296.—Mammary glands of weanling male mice dissected out, stained, and mounted whole without sectioning. *Top row*, From normal, intact, and untreated animals. Glands are rudimentary, unclubbed, and very slowly growing. *Lower three rows*, From totally hypophysectomized animals given 0·2 mg. pituitary growth hormone with ovarian hormones over a period of 5 days. Mammæ show clear evidence of rapid growth and a profusion of 'clubs', i.e., response limited to the initial mitotic phase of growth responsible for production of a branching duct system. (× 10.)

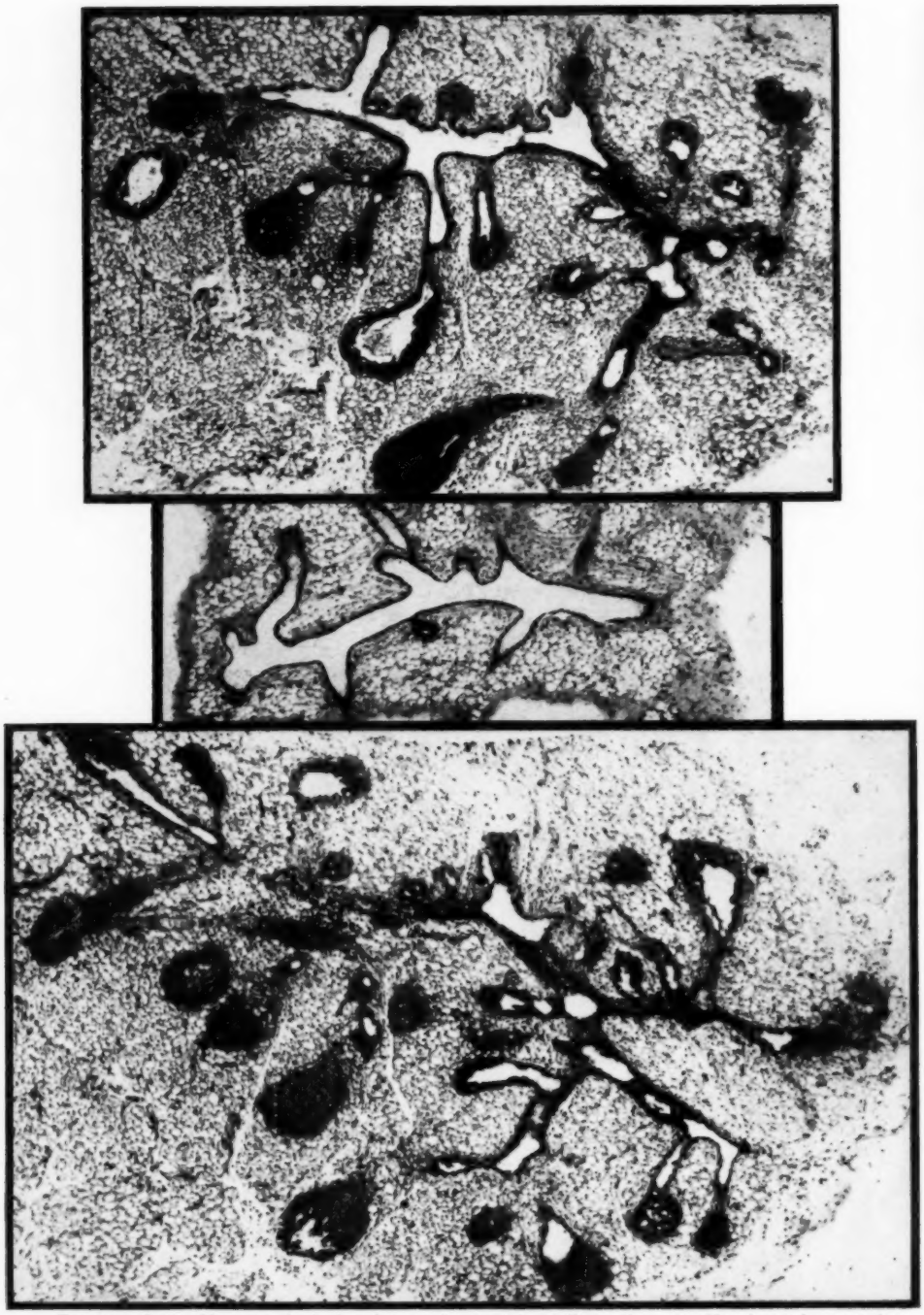

FIG. 297.—*Centre*, Mammary gland of an intact and untreated weanling male mouse. Note inconspicuous nuclear activity at the free ends of the slowly-growing duct branches. *Above* and *Below*, Mammary glands of a hypophysectomized weanling male mouse given prolactin, œstrone, and progesterone for 5 days. Glands are in the mitotic phase of growth. The free ends of all ducts terminate in 'clubs' composed of rapidly growing undifferentiated epithelium. (× 50.)

A

B

FIG. 298.—A, A dividing duct from the mamma of a normal intact and untreated weanling male mouse. Note that the single layer of duct epithelium is quiescent except at the free ends where the mild nuclear activity of normal growth can be seen. B, A prolific epithelial growth response artificially induced in a dividing duct from the mamma of a totally hypophysectomized weanling male mouse given pituitary growth hormone, œstrone, and progesterone twice a day for 5 days. When acting alone, neither the pituitary nor the ovarian component of this hormone combination was able to induce this response. (× 200.)

of normal breast growth is more intimately related to the basic problems of hormone-dependent breast cancer than the investigation of glandular differentiation and milk production. On this hypothesis growth hormone may eventually prove to be of fundamental significance in human breast cancer.

CONCLUSIONS

1. The rudimentary mammary glands of hypophysectomized weanling mice are remarkably responsive to the hormones contained in crude extracts of the human anterior pituitary provided that ovarian hormones are administered with them.

2. The mammary growth responses induced by these extracts are accompanied by a highly significant increase in body-weight.

3. Identical mammary and somatic growth responses can be induced by ovine growth hormone acting in synergism with ovarian hormones.

4. The mammary growth responses induced by human pituitary hormones and ovine growth hormones, when both are given with ovarian hormones over a period of 5 days, are limited to the formation of a duct system and are characterized by intense mitotic activity.*

* Previous experiments have shown that glandular differentiation can be induced in intact weanlings by the injection of prolactin with ovarian hormones over the same period.

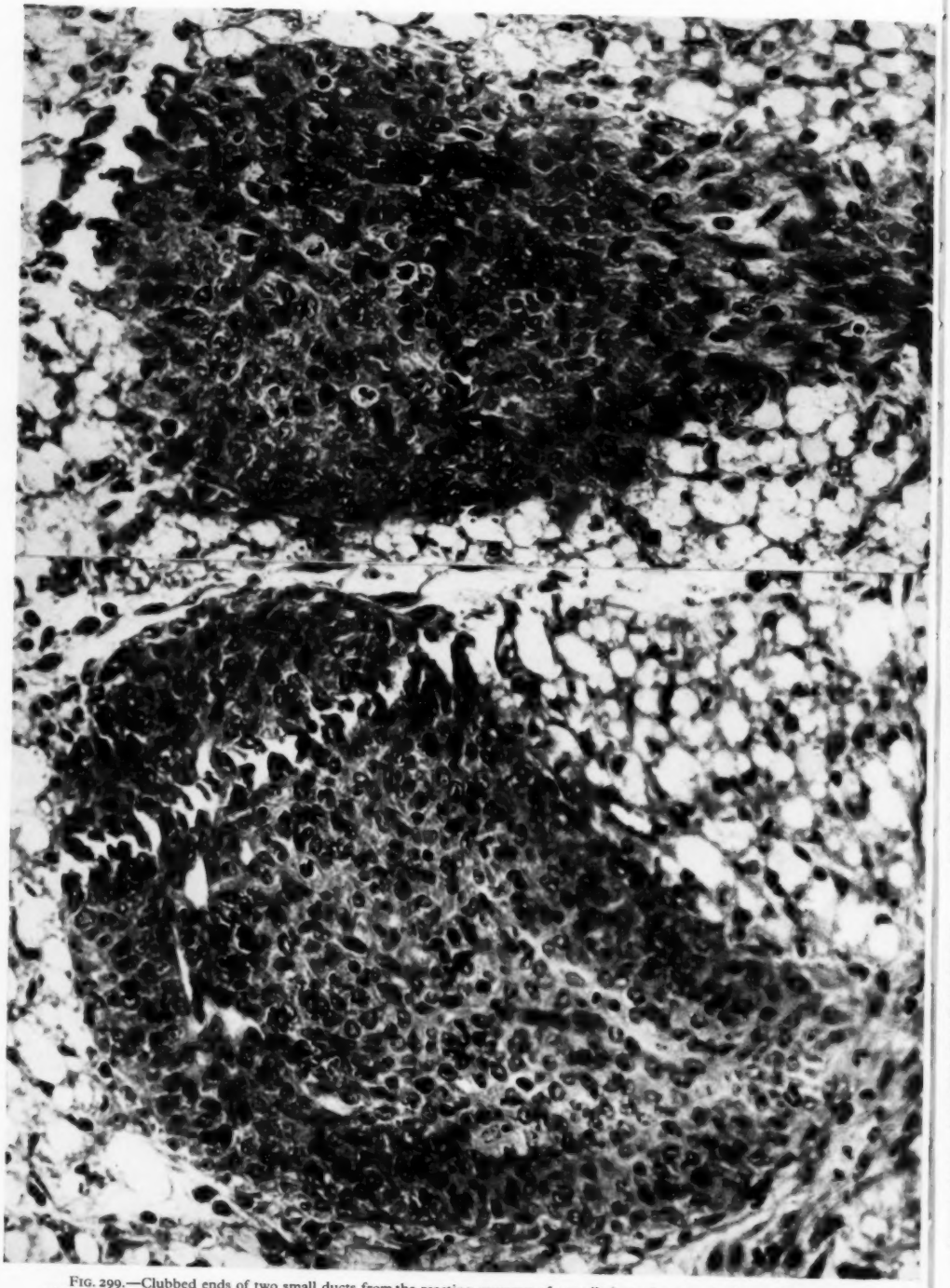

FIG. 299.—Clubbed ends of two small ducts from the reacting mammæ of a totally hypophysectomized weanling male mouse given prolactin with ovarian hormones for 5 days. The intensity of epithelial response is shown by total lack of differentiation and by nucleolar prominence and numerous mitotic figures. (× 400.)

5. The possible application of these observations to human breast cancer is discussed.

Acknowledgement.—Dr. C. C. Spicer is responsible for the statistical analyses and we are very grateful for his collaboration.

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THE EFFECT OF HYPOTHERMIA ON THE LESION OF EXPERIMENTAL RENAL ISCHÆMIA

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THE development of renal failure as an undesirable sequela of severe injury or of massive hæmorrhage has become well recognized through the work of Bywaters and Beal (1941) and Bywaters (1944), and the pathogical changes have been described by Shaw Dunn, Gillespie, and Niven (1941), Bywaters and Dible (1942), Lucké (1946), and by Sheehan and Moore (1953). The similarity between the morbid and functional changes in the 'shock kidney' and those produced by experimental renal ischæmia in animals has been commented on by various workers (Scarff and Keele, 1943; Badenoch and Darmady, 1947; Oliver, MacDowell, and Tracy, 1951; and Van Slyke, 1948). The essential lesion in both, a tubular necrosis, is generally considered to be the result of varying periods of renal anoxia.

In the following experiments a study has been made of the effect of hypothermia on the lesion produced by renal ischæmia in rats. Histochemical examination of two enzyme systems has also been carried out in an attempt to identify alterations in cell function which may precede morphological changes resulting from either ischæmia or hypothermia.

MATERIAL AND METHODS

Adult albino rats (approximate weight 200 g.) of both sexes were used throughout the experiments. Anæsthesia was induced and maintained by open ether at a depth sufficient to abolish the shivering response in the cooled animals. The left kidney was approached by the transperitoneal route and the renal circulation occluded by placing an atraumatic wire clamp across both artery and vein, care being taken to avoid the ureter. In all experiments the right kidney was used as a control. Hypothermia was induced by spraying ether on to the axillæ and groins of the anæsthetized animals, the temperature being reduced to 23° C. and maintained at that level for the rest of the experiment. The temperature changes were recorded on a rectal thermometer. The total number of animals used in these experiments was 83.

The animals were sacrificed at varying periods after operation, both right and left kidneys being removed for histological and histochemical studies. Each kidney was bisected in the coronal plane; one-half was prepared for routine staining by hæmalum and eosin; the other half was divided and one part fixed in cold acetone and subsequently embedded in paraffin wax. The remaining portion was placed in a test-tube and fresh frozen by a mixture of methanol and solid carbon dioxide at a temperature in the region of −70° C. Sections were cut at 10 μ in a freezing cabinet, placed on a slide, melted with the heat of the finger, and then dried at room temperature by means of a fan. These sections were then immediately incubated in media to demonstrate the succinic dehydrogenase system and non-specific alkaline phosphatase.

Succinic Dehydrogenase System.—The method used for demonstrating this enzyme system was a modification of that described by Rutenberg, Wolman, and Seligman (1953), but omitting magnesium sulphate and aluminium chloride from the incubating mixture. Incubation was carried out at 37° C. for 30 minutes. No difficulty in staining of these thin sections has been experienced, as was noted by Gomori (1952).

Non-specific Alkaline Phosphatase.—In all the specimens studied for this enzyme cold acetone fixed–paraffin embedded material was used, and in some instances fresh frozen sections cut at 10 μ were also incubated. The method used for demonstrating the enzyme was the modification of that of Manheimer and Seligman (1948) used by Burgos, Deane, and Karnovsky (1955), calcium α-naphthylphosphate and 5-chloro-O-toluidine (brentamine fast red TR salt—Imperial Chemical Industries) being respectively the substrate and azo-coupling agent used. The incubation was carried out at room temperature for 20–30 minutes. In all cases when comparative quantitative differences in enzyme content were being made between normothermic and hypothermic animals, material from both sources was incubated in the same mixture for the same period of time.

RESULTS

Normothermic Animals.—In one group of animals the renal pedicle was clamped for a period of 2 hours and survival allowed for varying periods

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of time (*Table I*). There was congestion of the renal parenchyma after 5 minutes' reflow, and in some of the animals, separation of the cells of the proximal convoluted tubules from their basement membranes (*Fig.* 300). Occasional glomeruli showed exudate in Bowman's capsule. After 24 hours' reflow widespread necrosis of the proximal convoluted tubules was evident and almost all the tubules appeared to have been uniformly involved. In a few cases, however, the distribution of the lesion was more focal and some proximal convoluted tubules were unaffected. Many of the cells had lost their nuclei and in others pyknosis was marked. The proximal convoluted tubule was now represented by uniformly staining eosinophilic debris (*Fig.* 301). Casts of shed cells were present in the loops of Henle and

FIG. 300.—Normothermic rat. Renal pedicle clamped 2 hours; 5-minute reflow. Separation of some proximal convoluted tubules from their basement membranes. H. and E. (× 144.)

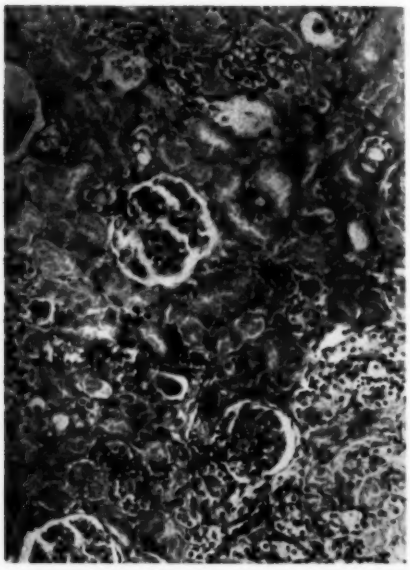


FIG. 301.—Normothermic rat. Renal pedicle clamped 2 hours; 48-hour reflow. There is widespread necrosis of proximal convoluted tubules and some distal convoluted tubules contain casts. H. and E. (× 108.)

Table I.—SUMMARY OF RESULTS—2 HOURS' RENAL ISCHÆMIA

DURATION OF REFLOW	ROUTINE STAINING		NON-SPECIFIC ALKALINE PHOSPHATASE		SUCCINIC DEHYDROGENASE SYSTEM	
	Normothermic	Hypothermic (23° C.)	Normothermic	Hypothermic (23° C.)	Normothermic	Hypothermic (23° C.)
5 minutes	Congestion of cortex, P.C.T.*—sleeve separation of occasional tubules	Normal appearance	P.C.T.—slightly diminished	P.C.T.—slightly diminished	Slightly diminished throughout kidney	Slightly diminished throughout kidney
48 hours	P.C.T.—uniform necrosis. Thick limb of loop of Henle—focal areas of necrosis. D.C.T.† and C.T.‡—casts present	Normal appearance	P.C.T.—necrotic debris stains strongly. No intracellular distribution	Normal distribution	P.C.T.—absent in necrotic tubules. Limb of Henle and D.C.T.—slightly diminished	Normal distribution
7 days	P.C.T.—dilated and lined by flattened cuboidal epithelium. D.C.T. and C.T.—occasional casts. Interstitial tissue—lymphocytic infiltration	Normal appearance	P.C.T.—absent in dilated tubules. D.C.T. and C.T.—occasional casts still stain	Normal distribution	P.C.T.—absent in dilated tubules. Limb of Henle and D.C.T.—normal distribution	Normal distribution

* P.C.T. = Proximal convoluted tubule. † D.C.T. = Distal convoluted tubule. ‡ C.T. = Collecting tubule.

eosinophilic casts in the distal convoluted and collecting tubules. Necrosis and regeneration of small groups of cells lining the thick limb of Henle were present in some cases (*Fig.* 302), but the lesion was minimal when compared with that in the proximal convoluted tubules. No lesions were noted in the glomeruli, distal convoluted tubules, or collecting tubules. The changes of necrosis were maximal at 48 hours. Occasional necrotic tubules contained deposits of calcium salts. Thereafter the stage of repair became evident

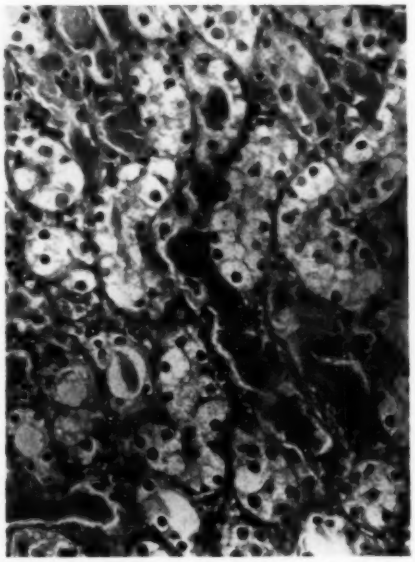


FIG. 302.—Normothermic rat. Renal pedicle clamped 2 hours; 48-hour reflow. Focal areas of necrosis of the cells lining the thick limb of the loop of Henle. H. and E. (× 252.)

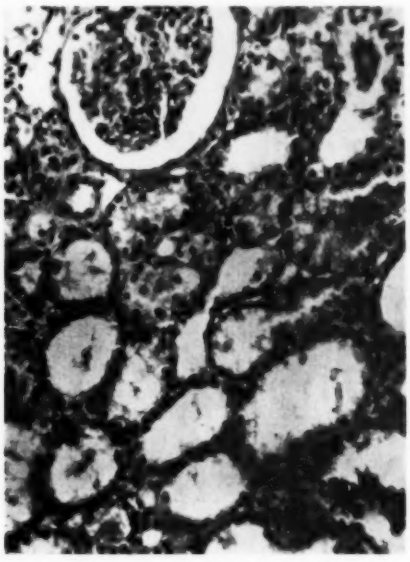


FIG. 303.—Normothermic rat. Renal pedicle clamped 2 hours; 7-day reflow. The proximal convoluted tubules are dilated and lined by a flattened cuboidal epithelium. H. and E. (× 204.)

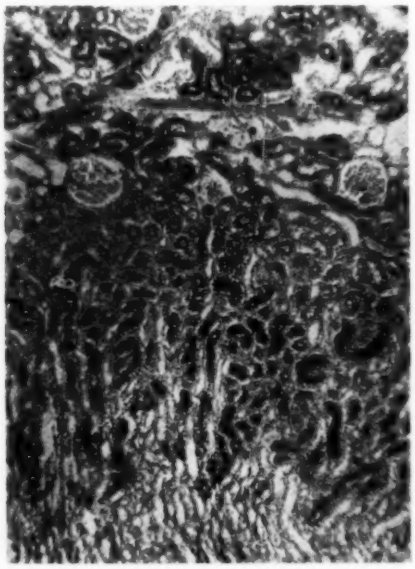


FIG. 304.—Normal rat kidney. Alkaline phosphatase preparation showing activity in the proximal convoluted tubule. It stains intensely the brush border of the straight portion. Azo-coupling technique. (× 30.)

FIG. 305.—Normal rat kidney. This preparation shows the activity of the succinic dehydrogenase system in the renal cortex. The glomerular tuft does not react. Neotetrazolium. (× 186.)

and at 7 days after clamping was well established. There was marked dilatation of many proximal convoluted tubules which were lined for the most part by a flat cuboidal epithelium (*Fig.* 303). Other proximal convoluted tubules had lost their lumina.

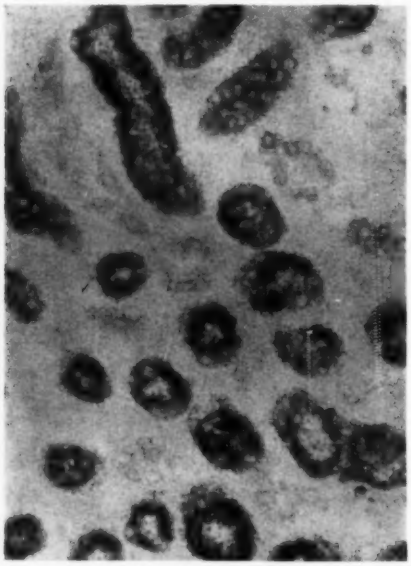
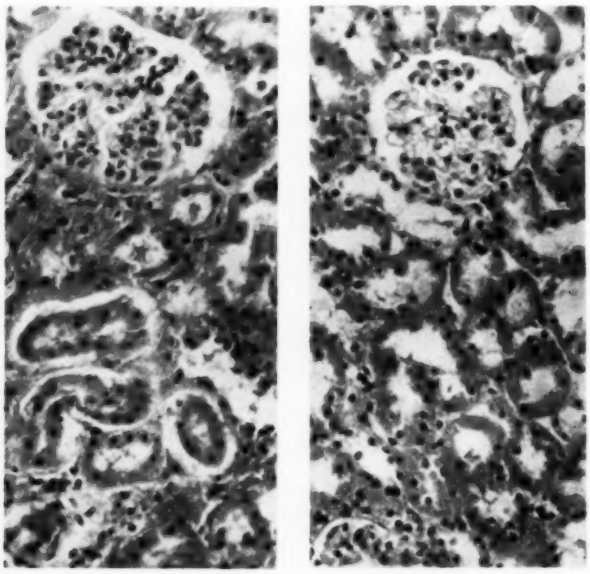


FIG. 306.—Normal rat kidney. The activity of the succinic dehydrogenase system is shown in the limbs of Henle in the renal medulla. Neotetrazolium. (× 186.)

Occasional casts were still present in the distal convoluted tubules and in the collecting tubules. The interstitial tissue was infiltrated with lymphocytes and occasional polymorphonuclear leucocytes. If the animals were allowed to survive for longer periods the kidney became smaller with a granular surface and the histological picture showed increasing atrophy of the proximal convoluted tubules. In another group, animals whose renal pedicles had been clamped for a shorter period of time but for longer than 30 minutes showed a similar sequence of changes as above, but more focal in distribution. Animals in which clamping had been carried out for 3–5 hours occasionally showed infarcts as well as the changes described above in the non-infarcted areas. In one of the rats whose renal pedicle had been clamped for 4 hours thrombus was found in a main branch of the renal vein in association with an infarct. Clamping the renal pedicle for 6 hours invariably produced an infarct of the whole kidney in which there were some surviving tubules beneath the capsule.

Hypothermic Animals.—Hypothermia was found to delay greatly the onset of changes which had been found in the normothermic animals. The majority of the rats whose renal pedicles had been clamped for 2 hours under hypothermia showed an apparently normal histological picture when allowed to survive longer than 48 hours. In a few instances the kidney showed focal areas of necrosis of the proximal convoluted tubules similar to that which was found in normothermic animals after the renal pedicle had been clamped for 1 hour. A period of 6-hours' renal ischæmia under hypothermia (23° C.) with 10 days' survival gave a histological picture

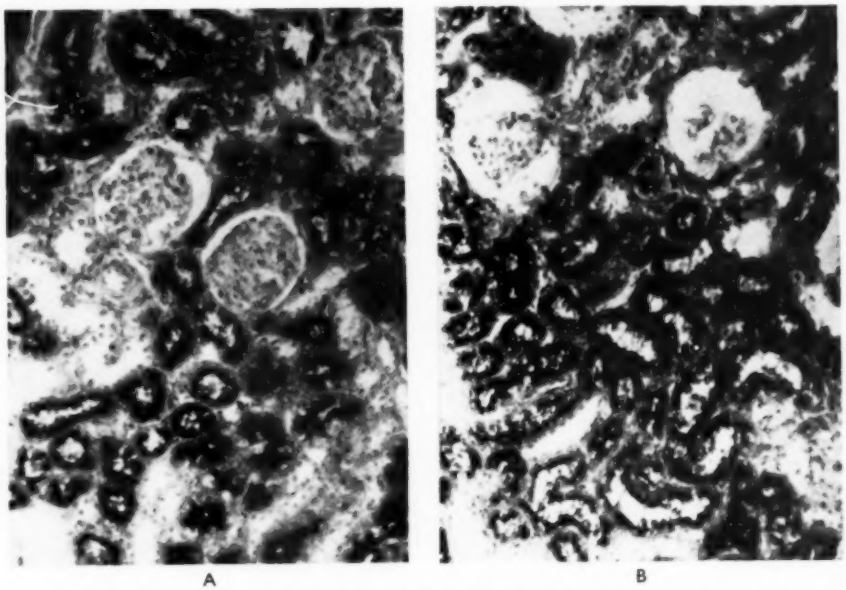


A B

FIG. 307.—A, Normothermic rat. Renal pedicle clamped 2 hours; 5-minute reflow. 'Sleeve' separation of proximal convoluted tubules from their basement membranes. B, Hypothermic rat. Renal pedicle clamped 2 hours; 5-minute reflow. Normal appearance. H. and E. (× 198.)

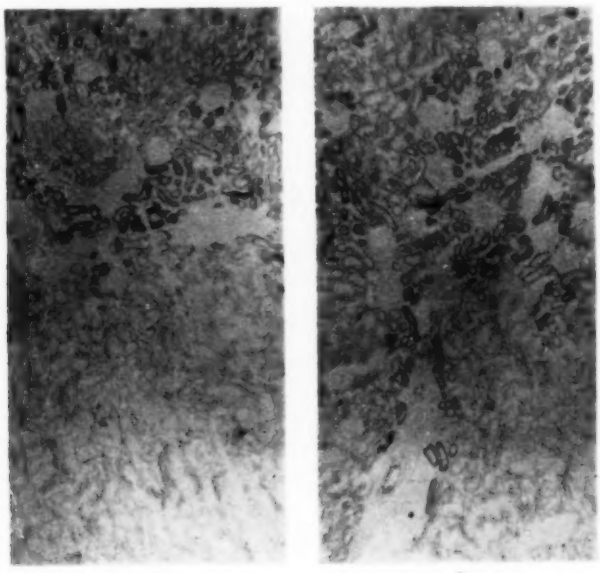
similar to that found in the normothermic animal which had had its renal pedicle clamped for 2 hours with a similar survival time.

Although practically no morphological changes were found in the kidneys clamped for 2 hours under hypothermia it was considered that there might be



A B

FIG. 308.—A, Normothermic rat. Renal pedicle clamped 2 hours; 5-minute reflow. Slight reduction in alkaline phosphatase activity. B, Hypothermic rat. Renal pedicle clamped 2 hours; 5-minute reflow. Slight reduction in alkaline phosphatase activity. Azo-coupling technique. (× 138.)

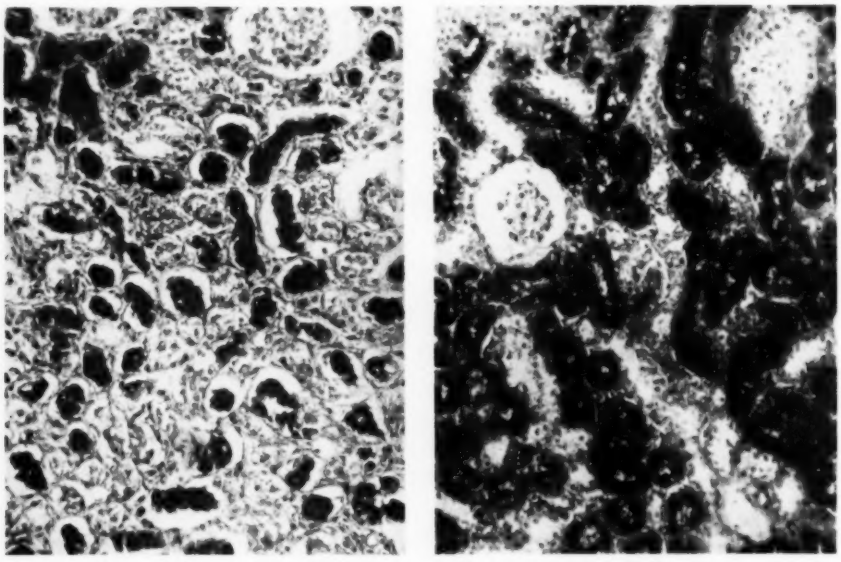


A B

FIG. 309.—A, Normothermic rat. Renal pedicle clamped 2 hours; 5-minute reflow. The activity of the succinic dehydrogenase system is diminished in both cortex and medulla. B, Hypothermic rat. Renal pedicle clamped 2 hours; 5-minute reflow. There is diminution in the activity of the succinic dehydrogenase system in cortex and medulla. Neotetrazolium. (× 24.)

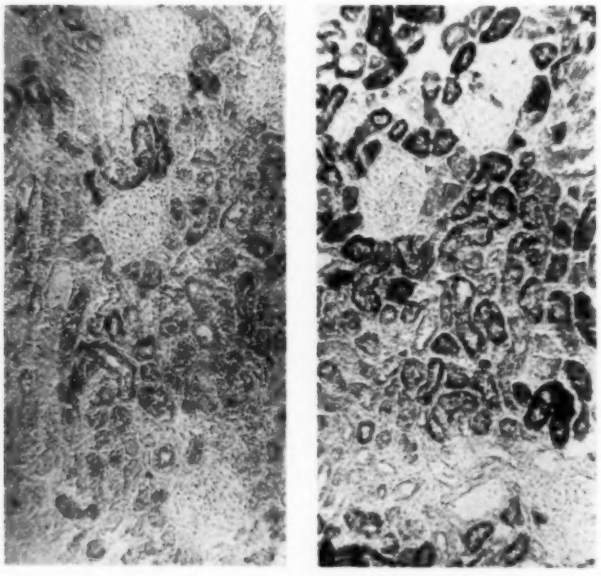
functional impairment of the tubules, and enzyme studies were undertaken to elucidate this point. The two enzymes used were non-specific alkaline phosphatase and the succinic dehydrogenase system.

Enzyme Studies.—Non-specific alkaline phosphatase in the rat kidney is present in the proximal convoluted tubule and in acetone fixed–paraffin embedded material stains the brush border most



A B

FIG. 310.—A, Normothermic rat. Renal pedicle clamped 2 hours; 48-hour reflow. The necrotic epithelium stains intensely in this alkaline phosphatase preparation. B, Hypothermic rat. Renal pedicle clamped 2 hours; 48-hour reflow. Normal distribution of alkaline phosphatase activity. Azo-coupling technique. (× 138.)



A B

FIG. 311.—A, Normothermic rat. Renal pedicle clamped 2 hours; 48-hour reflow. There is marked diminution in the activity of the succinic dehydrogenase system in the renal cortex. B, Hypothermic rat. Renal pedicle clamped 2 hours; 48-hour reflow. Normal activity succinic dehydrogenase system in the renal cortex. Neotetrazolium. (× 72.)

intensely (*Fig.* 304). In addition, we found that there was a diffuse but less intense cytoplasmic distribution in the cells of the convoluted portion of the proximal convoluted tubule. On this point our findings are in agreement with those of Longley and Fisher (1954), and are similar to those of Burgos and others (1955). When unfixed tissue was used there was a diffuse staining of the cells of both segments of the proximal convoluted tubule, no brush border distribution being present. Wachstein (1955) found a similar pattern using unfixed frozen sections.

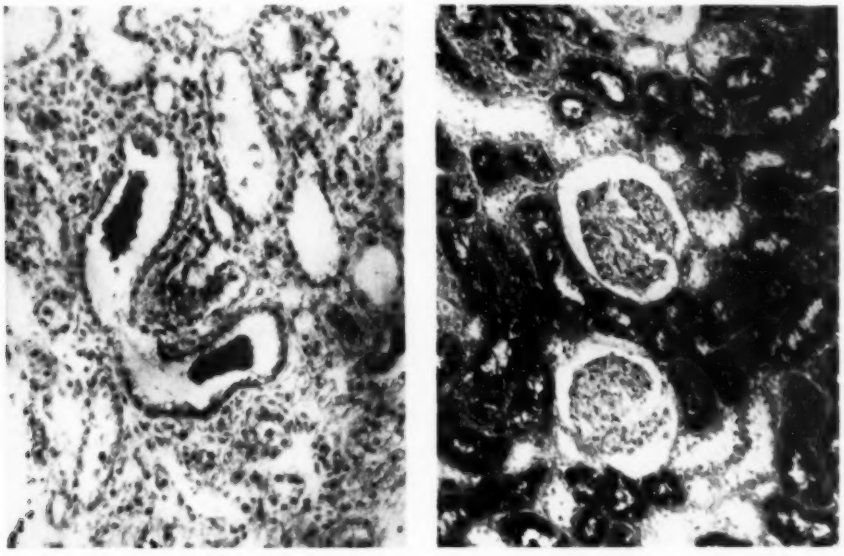
The succinic dehydrogenase system in the rat kidney is situated in the proximal and distal convoluted tubules (*Fig.* 305), and in the thick limb of the loop of Henle (*Fig.* 306).

The period chosen for clamping in the enzyme studies was 2 hours, as at this time maximal changes are evident in the proximal convoluted tubules in normothermic animals, and consequently some indication could therefore be obtained of the protective effect of hypothermia. Normothermic and hypothermic animals were killed at 5 minutes, 48 hours, and 7 days.

Examination of the right (unclamped) kidney histologically and histochemically after hypothermia showed no morphological alteration or diminution in the intensity of the staining reactions for the enzymes.

Five-minute Reflow.—There was congestion and some 'sleeve' separation of the proximal convoluted tubules of the normothermic animals (*Fig.* 307 A). The kidneys of the hypothermic animals were congested but otherwise normal (*Fig.* 307 B). Both normothermic (*Fig.* 308 A) and hypothermic (*Fig.* 308 B) animals showed a reduction in non-specific alkaline phosphatase and in the succinic dehydrogenase system (*Fig.* 309). The latter was also diminished in the thick limb of the loop of Henle and in the distal convoluted tubule.

Forty-eight-hour Reflow.—The necrotic epithelium stained intensely for non-specific alkaline phosphatase, but there was no selective distribution, as occurred normally (*Fig.* 310 A). The casts in the loops of Henle, distal convoluted tubules, and collecting tubules stained with a similar intensity. The hypothermic animals showed no abnormality in the distribution of this enzyme (*Fig.* 310 B). The succinic dehydrogenase system showed a normal pattern in the hypothermic animals both in cortex (*Fig.* 311 B) and medulla, whereas it was absent from the proximal convoluted tubules (*Fig.* 311 A) and diminished in the distal convoluted tubules and the ascending limb of the loop of Henle in the normothermic animals.



A B

FIG. 312.—A, Normothermic rat. Renal pedicle clamped 2-hours; 7-day reflow. Absence of alkaline phosphatase activity, but the cast in the dilated tubule stains. B, Hypothermic rat. Renal pedicle clamped 2 hours; 7-day reflow. Normal distribution of alkaline phosphatase activity. Azo-coupling technique. (× 138.)

Seven-day Reflow.—Non-specific alkaline phosphatase was completely absent from the proximal convoluted tubules of the normothermic animals, but the few remaining casts stained intensely (*Fig.* 312 A). In the hypothermic animals a normal distribution of this enzyme was obtained (*Fig.* 312 B). In the normothermic group the succinic dehydrogenase system was greatly diminished in the dilated tubules (*Fig.* 313 A), whereas the hypothermic group had a normal pattern (*Fig.* 313 B).

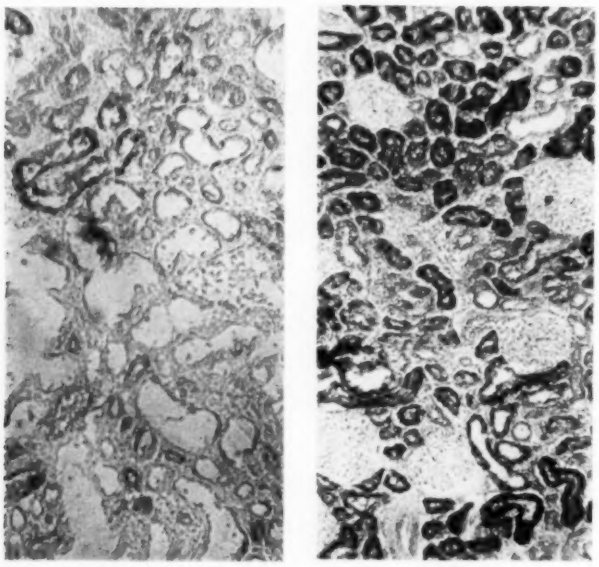
DISCUSSION

The lesion in the nephron following temporary complete renal ischæmia was found to be maximal in the proximal convoluted tubule, although a focal

lesion in the thick limb of the loop of Henle was occasionally observed. The latter resembles the patchy disruptive lesion of 'tubulorhexis' of Oliver and others (1951) and confirms that in renal ischæmia all parts of the nephron may be involved.

A diffuse necrosis followed a period of ischæmia of 2 hours' duration, and a more patchy lesion was evident after shorter periods of occlusion. Interruption of the circulation beyond 2 hours tended to give rise to areas of infarction. The changes in the proximal convoluted tubules were similar to those found by Koletsky and Gustafson (1947), Koletsky (1954), and by Gowing and Dexter (1956) in the rat, and by Scarff and Keele (1943) in the rabbit. Burwell (1955) working with rabbits found that the initial ischæmic changes occurred in the medullary segment of the proximal convoluted tubule. Badenoch and Darmady (1947), however, experimenting with rabbits, found that the earliest changes occurred in the limbs of Henle. Oliver and others (1951), using a microdissection technique, found that all parts of the nephron of the dog were involved in ischæmic damage. Bywaters and Dible (1942) describe the renal lesion in traumatic anuria in man as falling with especial severity on the ascending limb of Henle and the second convoluted tubule. This picture is similar to that obtained experimentally by Badenoch and Darmady in rabbits. They attribute the aetiology to an incomplete renal ischæmia, the site of the lesion in the tubule being the last portion to be supplied by blood from the renal circulation.

The lesion observed resembles the proximal convoluted tubular necrosis described by Sheehan and Moore (1952). They regard it as the earliest stage of the lesion in the kidney following concealed accidental hæmorrhage, and attribute the lesion to a spasm of the glomerular capillaries lasting about three hours. Dible (1953) states that the earliest lesion which he has noted is a limited necrosis of the first convoluted tubule in its descending portion.



A B

FIG. 313.—A, Normothermic rat. Renal pedicle clamped 2 hours; 7-day reflow. The activity of the succinic dehydrogenase system in the renal cortex remains diminished and is almost completely absent from the dilated tubules. B, Hypothermic rat. Renal pedicle clamped 2 hours; 7-day reflow. Normal activity succinic dehydrogenase system. Neotetrazolium. (× 72.)

Oliver and others also found damage to the proximal convoluted tubule in the lesions they called 'ischemuric tubulorhexis'. Koletsky (1954) has noted that the terminal segment of the proximal convoluted tubule is especially involved in temporary complete renal ischæmia, and Burwell (1955) reports that the earliest changes are found at this site. Thus the experimental evidence shows that the earliest change of renal ischæmia is in the terminal segment of the proximal convoluted tubule, and since the earliest change in acute tubular necrosis is also at this site, it is probable that the initial changes in man are also due to ischæmia. The aetiology of the subsequent changes in traumatic renal anuria and these other conditions listed as "lower nephron nephrosis" by Lucké (1946) remains obscure.

The succinic dehydrogenase system and non-specific alkaline phosphatase were chosen for study because of their distribution in the nephron. Moreover, the disappearance of the former indicates necrobiotic changes before they may become demonstrable with routine staining techniques (Wachstein, 1955), and it has been shown by Berg and Levinson (1952) that reduction of alkaline phosphatase activity following experimental shock in dogs induced by *Clostridium perfringens* toxin appeared to

parallel mitochondrial changes. Thus, alteration in enzyme staining could be used both for information regarding the ischæmic lesion and also to demonstrate any changes in the right kidney which might result from hypothermia.

Immediately after the ischæmic episode in normothermic and hypothermic animals there is a uniform reduction in enzyme staining—it requires the 'reflow' to produce the sequence of necrobiotic changes in the tubules. In the hypothermic animals after 48 hours' reflow the majority of the tubules have regained their normal distribution of enzymes, whereas in the normothermic animal there is absence of the succinic dehydrogenase system and non-specific alkaline phosphatase from the cells, although the presence of the latter is noted in casts. In the regenerating tubules of the normothermic animal after 7 days' reflow both enzymes are still absent, and Oliver (1953) has pointed out that the marked diminution in enzyme activity in regenerating cells may well explain the impairment of renal function which is observed in patients who survive an acute attack of anoxic anuria.

During controlled cooling the reduction in oxygen demand is much greater than the reduction in oxygen availability (Delorme, 1952), and tissues can withstand periods of ischæmia which would induce permanent damage at normal temperature. As in Gowing and Dexter's (1956) experience, some of our hypothermic animals had uncontrolled shivering for short periods of time, and the increased demand for oxygen which this entails probably explains the focal areas of necrosis found in these animals. That hypothermia may in itself induce certain irreversible changes has been suggested by Knocker (1955), who claimed to have identified histopathological changes in the liver, kidneys, and adrenals of dogs which were subjected to hypothermia (25° C.). Sarajas, Senning, and Kaplan (1956) presented evidence of histological damage in the ventricular wall of dogs which had been subjected to a range of hypothermia varying from 29° C. to 17° C. Earlier investigation by Sarajas (1956) had shown no evidence of thrombotic or embolic phenomena in the coronary vascular bed, and the possibility of the changes being due to a relative myocardial hypoxia is discussed. Whatever the precise cause of the myocardial damage may be, Sarajas and others conclude that they have demonstrated a pathogenetic relationship between the lesions and the induction of a state of acute experimental hypothermia. Contrary opinion has been expressed by Swan and Zeavin (1954) and by Delorme (1952), who found no evidence of histological damage in any tissue following cooling, and suggested that any functional changes that did occur were completely reversible. In the present series, the unclamped right kidneys were examined histologically and histochemically in each case and in no instance, even after a period of 6 hours' cooling (23° C.), did we find any evidence of tissue damage by routine staining methods, or any indication of impaired functional activity as evidenced by diminished enzymatic staining with the *in vitro* techniques.

SUMMARY

1. The left renal vascular pedicle was clamped for varying periods of time in normothermic and hypothermic rats. The right kidney was used as a control.

2. In the normothermic animals clamping of the pedicle for a period of 2 hours produced a necrosis of proximal convoluted tubules, which in the stage of repair were lined by flattened cuboidal epithelium deficient in enzyme content. A focal lesion in the thick limb of the loop of Henle was occasionally observed.

3. Hypothermia greatly delayed the onset of the lesion and in the animals which were cooled and had their pedicles clamped for 2 hours the majority of the tubules showed no morphological damage or diminution in enzyme content.

4. Hypothermia did not produce morphological damage or diminution in enzyme content of the control right kidney.

Acknowledgement.—We wish to express our thanks to Professor T. Symington of the St. Mungo-Notman Chair of Pathology, The University of Glasgow, for his assistance in this work.

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THE INHIBITORY ACTION OF LOCALLY APPLIED ANTIHISTAMINE ON THE GASTRIC SECRETION OF ACID AND PEPSIN INDUCED BY MEAT AND INSULIN IN DOGS

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In previous papers we have shown that in vagally denervated (Heidenhain) pouches in dogs, the local application of an antihistamine to the pouch mucosa will inhibit gastric secretion induced by histamine by peripheral parasympathetic stimulation and by the release of the antral hormone (Kay and Forrest, 1956 a, b, 1957).

Experiments are now described in which the effect of a locally applied antihistamine has been determined on the secretory response of vagally innervated gastric pouches to a meal of meat and to insulin hypoglycæmia.

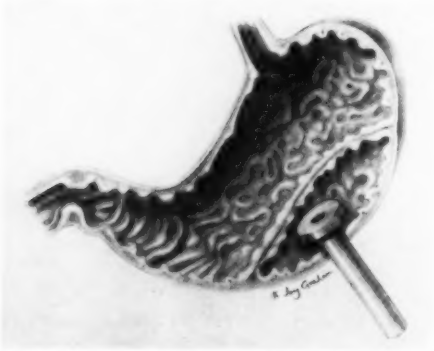

FIG. 314.—Mucosal septal pouch of Hollander-Jemerin type.

METHOD

Three dogs with vagally innervated mucosal septal pouches (Hollander-Jemerin type) were studied (*Fig.* 314). Dogs were fasted for 20–24 hours before each test.

In a first series of experiments the stimulus of pouch secretion was the ingestion of a constant weight (½ lb.) of a proprietary preparation of horse meat. Juice was collected from the pouches at intervals of 15 minutes for a period of 4 hours. In four control tests on each dog, meat was given without prior irrigation of the pouch; in four further tests the pouch was irrigated for 30 minutes with a solution of promethazine hydrochloride (6 mg. per ml. in 0·9 per cent saline) and allowed to drain for 15 minutes before giving the meat. In an additional three tests in one dog the concentration of promethazine in the irrigating fluid was increased to 10 mg. per ml.

In a second series of experiments pouch-secretion was stimulated by the intravenous injection of insulin (2 units per kg. body-weight) and juice collected at 15-minute intervals for 3 hours. As this dose of insulin had previously been found to produce adequate hypoglycæmia and a good secretory response, serial estimations of blood-sugar were not performed in the present experiments. In each dog three insulin tests were performed with, and three without, prior irrigation of the pouch with promethazine hydrochloride (6 mg. per ml. in 0·9 per cent saline) for 30 minutes.

In all tests the volume of each 15-minute specimen was measured in millilitres and the concentration of free hydrochloric acid determined by titration with decinormal sodium hydroxide using Topfer's solution as indicator. From these values the output of hydrochloric acid was calculated in milli-equivalents per 15 minutes. Specimens of hourly juice were obtained by pooling aliquots of each 15-minute collection. The concentration of pepsin in these pooled samples was estimated by the method of Hunt (1948) using pooled dried human plasma as substrate. The peptic activity was expressed in milligrams of tyrosine-like substances liberated from the substrate per millilitre of juice, and the product of the hourly volume of juice and its peptic activity represents the output of pepsin in milligram tyrosine equivalents per hour.

To obtain a statistical comparison of the secretory responses in the control and promethazine tests, the arithmetic means of the logarithms of the total outputs of juice, acid, and pepsin were compared by an analysis of variance.

Table I.—THE EFFECT OF PROMETHAZINE IRRIGATION (6 MG./ML.) ON THE SECRETORY OUTPUT FROM VAGALLY INNERVATED POUCHES IN RESPONSE TO A MEAL OF MEAT (*Each Result is the Mean of* 4 *Tests*)

Dog	Volume of Juice ml. per 4 Hr.		Output of HCl mEq. per 4 Hr.		Output of Pepsin mg. Tyrosine per 4 Hr.	
	Control	Promethazine	Control	Promethazine	Control	Promethazine
A	61·0	57·3	7·4	2·5	937	674
B	69·0	41·2	8·4	1·3	590	883
C	54·2	20·9	5·4	0·6	724	223

RESULTS

Meal of Meat.—In all tests in the 3 dogs, the local application of promethazine hydrochloride in a concentration of 6 mg. per ml. produced a profound

inhibition of the output of acid secreted in response to the ingestion of the meal of meat. The mean acid output during the 4 hours of the tests following the promethazine irrigation was 20 per cent of the control values, and this reduction is of statistical significance ($P<0.01$). The volume of juice secreted

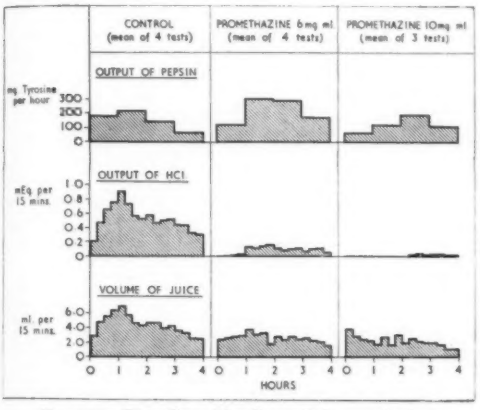

FIG. 315.—The effect of locally applied promethazine on the secretory response of a mucosal septal pouch to meat in a dog.

was inhibited to a lesser degree (64 per cent of the control values), but this reduction was also significant ($P<0.01$). On the other hand, the overall reduction of the output of pepsin in the tests following promethazine irrigation to 84 per cent of the control values was not of significance ($P>0.1$). (*Table I.*)

In the one dog so tested, increasing the concentration of promethazine in the irrigating solution to 10 mg. per ml. reduced the secretion of acid to 1 per cent of the control values. In these tests the reduction of the volume of secretion and output of pepsin were to 51 per cent and 81 per cent of the control values respectively (*Fig.* 315).

It is concluded that the local application of promethazine selectively inhibited the acid output of a vagally innervated pouch of the stomach stimulated by the ingestion of a meal of meat.

Insulin Hypoglycæmia.—The secretion of acid from the vagally innervated gastric pouches in response to insulin hypoglycæmia was entirely abolished by the local application of promethazine hydrochloride in a concentration of 6 mg. per ml. The volume of juice secreted and the pepsin output were also significantly reduced, the volume to 49 per cent ($P<0.001$) and the output of pepsin to 6 per cent ($P<0.001$) of the control values (*Table II* ; *Fig.* 316). It was noted that a more profound state of hypoglycæmia was produced by the insulin when the pouch had been previously irrigated with promethazine solution. On several occasions the dogs collapsed and developed convulsions necessitating resuscitation

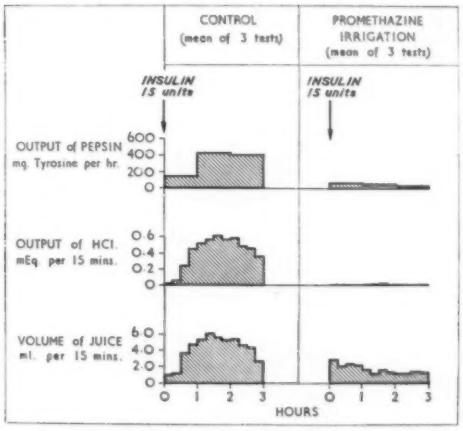

FIG. 316.—The effect of locally applied promethazine on the secretory response of a mucosal septal pouch to insulin hypoglycæmia in a dog.

with intravenous glucose solution. On no occasion was this necessary during the performance of the control tests.

It is concluded that locally applied promethazine will abolish the secretion of acid and significantly reduce that of juice and pepsin from vagally innervated pouches stimulated by insulin hypoglycæmia.

Table II.—THE EFFECT OF PROMETHAZINE IRRIGATION (6 MG./ML.) ON THE SECRETORY OUTPUT FROM VAGALLY INNERVATED POUCHES IN RESPONSE TO INSULIN HYPOGLYCÆMIA
(*Each Result is the Mean of* 3 *Tests*)

Dog	Volume of Juice ml. per 3 Hr.		Output of HCl mEq. per 3 Hr.		Output of Pepsin mg. Tyrosine per 3 Hr.	
	Control	Promethazine	Control	Promethazine	Control	Promethazine
A	50·0	19·7	4·7	0	979	149
B	18·0	11·5	1·4	0	353	40
C	14·4	6·3	0·5	0	331	25

DISCUSSION

Our results indicate that the local application of an antihistamine to the gastric mucosa effectively inhibits the acid secretory response following the ingestion of a meal of meat. In a vagally innervated pouch of the stomach, both the nervous and hormonal phases of gastric secretion are activated when food is eaten, and the high potency of meat as a stimulus for acid secretion is confirmed by the need to increase the concentration of promethazine in the irrigating solution to 10 mg. per ml. to obtain complete inhibition. The absence of a significant effect on the secretion of pepsin agrees with our previous findings from peripheral parasympathetic stimulation

of pouch secretion (Kay and Forrest, 1956 b) and allows the conclusion to be drawn that the antihistamine selectively inhibits the acid-secreting mechanism. In the present experiments the small reduction in pepsin output following the promethazine irrigation is adequately accounted for by the reduction in the volume of juice secreted.

In the second group of experiments in the same animals, the local application of the antihistamine completely abolished the acid secretory response to insulin hypoglycæmia. Contrary to our findings with other stimuli, a profound depression of pepsin secretion also occurred. That the insulin test provides an unsatisfactory quantitative measure of gastric secretory response is evident from its ability to *inhibit* as well as stimulate the secretion of acid and of pepsin by the stomach (Burstall and Schofield, 1951 a, b; Karniven and Karvonen, 1952). Furthermore it has been shown that this inhibitory action is independent of the innervation of the stomach and probably due to a depression of metabolic activity resulting from hypoglycæmia (Forrest and Code, 1954).

In the present experiments it was noted that the injection of the same dose of insulin produced more severe hypoglycæmic symptoms after promethazine irrigation than in the control tests, presumably due to absorption of promethazine from the gastric pouch. Glucose administration was regularly required after promethazine irrigation, and on several occasions had to be given repeatedly to restore the animal to consciousness. It is suggested that, in the promethazine tests, the dogs developed a degree of hypoglycæmia which would not support continuation of any form of gastric secretion and that no valid conclusions can be made.

It has been shown in this series of studies that locally applied antihistamine selectively inhibits the secretion of acid from the stomach, whether this is stimulated by the administration of histamine, by the parasympathomimetic drug carbaminoyl-β-methyl-choline, by gastrin release, or by the physiological stimulus of a meal of meat, and that this effect is not the result of a local anæsthetic or atropine-like activity. While the results of these studies support the view that histamine normally participates in all phases of gastric secretion, they do not provide conclusive evidence.

Proof that promethazine acts solely by antagonizing histamine must await the isolation of a pharmacologically specific antihistamine.

SUMMARY

In 3 dogs with vagally innervated pouches of the stomach, the effect of locally applied promethazine hydrochloride has been determined on the secretion of acid and pepsin in response to a meal of meat and insulin hypoglycæmia. The results support our previous findings that the antihistamine selectively inhibits the secretion of acid by the stomach.

Acknowledgements.—We wish to thank Professor Weipers and Mr. Donald Lawson of the University Veterinary Hospital, Glasgow, for assistance with the care of the animals. The antihistamine used in this series of experiments was kindly supplied by May & Baker Ltd.

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SHORT NOTES OF RARE OR OBSCURE CASES

A CASE OF BILATERAL OPEN PNEUMOTHORAX, CUT THROAT, AND PENETRATING ABDOMINAL INJURY WITH SURVIVAL

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FOR many years it was considered that bilateral open pneumothorax was incompatible with life. Graham and Bell (1918) stated that bilateral open pneumothorax was compatible with life, provided that the openings were small. As their experiments were carried out on human cadavers, in which the mediastinum is very fixed, and on dogs, in whom the mediastinum is very much more mobile than in the living human, it was held by many physiologists that their results were not necessarily applicable to human respiratory physiology.

Two cases of transthoracic impalement by iron bars are reported in the literature (Schmitt, 1949; Alessi, 1952). In these cases both pleural cavities were punctured; it is probable that the openings were relatively small, i.e., fulfilling the conditions laid down by Graham and Bell; both patients survived. No other cases have been reported.

In the case reported here the patient survived after bilateral open pneumothorax, cut throat, and penetrating abdominal injury.

CASE REPORT

An Indian girl, aged 9 years, was admitted to the General Hospital, Singapore, on Oct. 5, 1956. She had been assaulted two hours previously by her stepfather, who had used as a weapon a penknife with a 3-in. blade.

When first seen in the Casualty Department she was fully conscious, very shocked, and definitely cyanosed. She lay curled up on her right side and became very distressed when attempts were made to turn her on her back. The alæ nasi were working rapidly. Respiratory rate was 50 per minute, pulse 150; temperature 96·5° F.; blood-pressure 90/40.

She had the following wounds:—

1. A 5-in. wound across the throat, at the level of, and down to, the hyoid bone.

2. A 5-in. wound across the throat, parallel to the upper one, at the level of the cricothyroid membrane; this cut had divided both the strap muscles and had severed the larynx for four-fifths of its anteroposterior depth, through the membrane. The carotid sheath of each side was exposed but undamaged. The child was breathing entirely through this wide, open wound.

3. A wound across the back of the neck about 4 in. long and rather to the left side; it was about 2 in. deep throughout and in the midline had reached the ligamentum nuchæ.

4. An 8-in. wound in the left side of the chest traversing the 5th–6th intercostal space; the pleura was opened throughout the length of the incision and the heart was clearly visible without need of retraction.

5. A 4-in. wound on the right side through the anterior end of the 7th–8th intercostal space; the pleura was opened throughout the length of the wound.

6. A 4-in. wound, horizontal and to the right of the umbilicus, and a 2-in. wound at the same level to the left of the umbilicus. These wounds were no deeper than the anterior rectus sheath.

7. A number of superficial skin wounds (? tentative cuts) on the neck, over the sternum, and on the right thigh.

In general, all the wounds appeared to have bled remarkably little. The chest wounds were covered with dressings, wool, and adhesive plaster. The child was placed in an oxygen tent, lying on her right side, and was given atropine, 1/100 gr. by intramuscular injection. Blood was taken for cross-matching and an intravenous transfusion of dextran started.

Slight improvement in the child's general condition occurred and shortly after she was removed to the operating theatre.

AT OPERATION.—The exposed laryngo-tracheal junction was sprayed with cocaine and a cuffed endotracheal tube inserted. Gas, oxygen, and ether were administered and as soon as the lungs inflated there was a definite improvement in the pulse, which became slower and of better volume. The wound in the left chest was first dealt with. Inspection within the thorax did not reveal any damage to pericardium or left lung and there was no evidence of intercostal arterial hæmorrhage. The left lung was fully expanded; the muscles were closed with a continuous catgut suture and the skin with continuous nylon, after insertion of a small drainage tube through a stab incision at a lower level. The right intercostal wound was next dealt with. On inspection, the gall-bladder was found to be prolapsed through the wound. The opening in the pleura was sufficient to admit four fingers. The gall-bladder was carefully reduced through a wound in the diaphragm large enough to admit two fingers. The right lower lobe was found to expand fully and there was very little blood in the pleural cavity. The tear in the diaphragm was repaired and the chest wound was then closed in two layers, after insertion of a stab drain through the 9th–10th intercostal space in the mid-axillary line. Both drainage tubes were connected to an under-water seal.

The abdominal wounds were examined and found to extend only to the anterior rectus sheath on either side; they were covered with sterile gauze and an upper right paramedian incision made. Laparotomy revealed no blood in the peritoneal cavity and no damage to the liver or other viscera. The incision was closed and the superficial wounds sutured. The minor cuts were dressed with flavine and the posterior neck wound was carefully cleaned and explored: the deep muscles and fascia were repaired with catgut and the skin closed with nylon. The operation

FIG. 317.—Patient three months after operation. Keloid tendency common in Eastern races noticeable in scars.

took about 1½ hours and during this time the child received 1½ pints of blood.

The patient was returned to the ward with a tracheotomy tube in the partially closed lower neck wound. Her general condition was good and the air entry in both lungs satisfactory. Two hours after operation the temperature had risen to 99·5° F., the pulse-rate was 120 per minute with a good volume, and respiration 38 per minute.

Forty-eight hours after operation the child was given a short general anæsthetic and a formal tracheotomy was done through a separate incision. The wound at the tracheo-laryngeal junction was sutured with fine catgut and the skin edges loosely approximated; at the same time, the lungs having fully expanded clinically and radiologically, the chest tubes were removed and the wounds sealed.

The child made an excellent and rapid recovery, the tracheotomy tube was removed three days later, and all the wounds healed by first intention, with the exception of one of the superficial abdominal wounds which suppurated for a few days. Chest radiography ten days after operation confirmed full expansion of the lungs.

The accompanying photographs show the child three months after operation (*Fig.* 317); they illustrate well the common keloid tendency in Eastern peoples. Three months after the event the child seemed well, cheerful, and happy. According to the mother and the Social Welfare Department she showed no emotional instability and was eating and sleeping well.

DISCUSSION

The fact that this child survived such terrible injuries is remarkable and, indeed, probably unique. Schmitt (1949) and Alessi (1952) each described a case of severe transthoracic impalement by an iron bar in which both pleural cavities were opened; the patients made an uninterrupted recovery. Graham and Bell (1918) stated, as a result of their experiments on dogs and human cadavers, that bilateral pneumothorax was compatible with life if the openings were small. In the case under discussion the openings were large, particularly on the left.

In this connexion, it is interesting that the child was able to relieve some of her respiratory distress by lying on her right side, presumably blocking off the smaller of the openings into the pleura by so doing, and also that the gall-bladder was found prolapsed into the external wound partially blocking it; no doubt both these factors helped the patient to survive the two hours before treatment began. Graham and Bell further calculated that owing to the elasticity of the lungs and frictional resistance in the air passages it is considerably easier for air to enter through a large pneumothorax wound than through the trachea, and that for a patient who could increase his tidal air to a vital capacity of 3500 c.c. the largest size of opening into *one* pleural cavity, compatible with life, is 5 × 10 cm. or 50 sq. cm. The two openings in this child's chest were approximately 20 cm. × 2·5 cm. = 50 sq. cm. on the left and 10 cm. × 1·25 cm. = 12·5 sq. cm. on the right. The patient, by lying on the right side and with the aid of the prolapsed gall-bladder, had successfully blocked the opening in the right chest. Thus, according to Graham and Bell's hypothesis, the child should have been able to survive a few hours with such a large opening if she was capable of increasing her tidal air to a vital capacity of 3500 c.c., but this figure, in a child of 9 years of age, would seem to be almost impossible. There is, however, another factor to be taken into consideration, namely, that the patient had a laryngotomy from the moment of injury.

Carter and Guiseffi (1951) have pointed out the usefulness of tracheotomy in crush injuries of the chest. They state that the effect of tracheotomy is physiological and mechanical. Physiologically the effect is to reduce the amount of dead space in the respiratory tree with a resulting increase in effective ventilation, and mechanically, to reduce the frictional resistance in breathing on both inspiration and expiration. As a result, therefore, of the traumatic laryngotomy at the time of injury the child would not have had to increase the tidal air to a vital capacity of 3500 c.c. in order to survive.

It is not possible to say what volume of tidal air would be necessary, but it seems that the child's survival does not contradict Graham and Bell's hypothesis, and that the concurrent injury to the larynx was an aid to the patient's survival.

Graham and Bell (1918) noted a marked fall in temperature in dogs with a large open pneumothorax, in fact, 3·5° F. in 45 minutes. This patient's temperature on admission was 96·5° F., i.e., after two hours of open pneumothorax; the temperature rose to 99·5° F. two hours after operation. This fall in temperature was not as marked as in Graham and Bell's dog experiments, but this could be accounted for by the fact that the patient was covered by a blanket in the ambulance and that the shade temperature on this particular day was 86° C.

SUMMARY

1. A case is recorded of survival after bilateral open pneumothorax, cut throat, and penetrating abdominal injury.

2. The findings in the case substantially support the hypotheses of Graham and Bell in 1918, made as a result of experiments on dogs and human cadavers.

3. The concurrent laryngotomy is shown to have aided the patient's survival.

4. The literature is reviewed.

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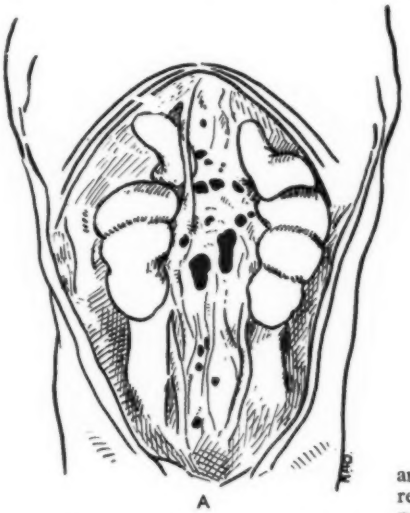
A PARAGANGLIOMA CAUSING PAIN RESEMBLING RENAL COLIC

By MICHAEL C. OLDFIELD and G. WILSON, Leeds

Zuckerkandl (1901) described collections of extra-adrenal chromaffin cells in the neighbourhood of the inferior mesenteric artery of the human fœtus and adult; subsequently these have often been referred to as the 'organs of Zuckerkandl'. Later, more complete descriptions of the extra-adrenal chromaffin tissue were published by Kohn (1903), Iwanow (1930, 1932), and Coupland (1952, 1954), who showed that collections of phæochromocytes were present in association with all parts of the pre-aortic sympathetic plexus in the fœtus and young child and referred to these as either 'paraganglia' or 'para-aortic bodies'. (*Fig.* 318.)



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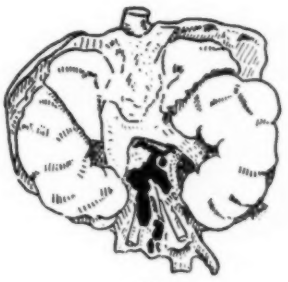

B

Fig. 318.—The organs of Zuckerkandl and the paraganglia in A, an 8·4 cm. fœtus (chromaffin tissue shaded black) and in B, a 3¾ lb. premature infant (chromaffin tissue shaded black). (*Drawings reproduced from photographs by kind permission of Dr. R. E. Coupland of the Anatomy Department of the University of Leeds.*)

In the fœtus the organs of Zuckerkandl have been shown to contain an appreciable quantity of noradrenaline (West, Shepherd, Hunter, and MacGregor, 1953; Coupland, 1953) and it seems probable that they supply this pressor amine to the circulation. By comparison with the adrenal medulla the extra-adrenal chromaffin tissue develops precociously during fœtal life and at birth forms the greatest part of the chromaffin tissue. During the first three years of life the adrenal medulla increases in size rapidly and reaches maturity, while the para-aortic bodies, including the organs of Zuckerkandl, show little change. The extra-adrenal chromaffin tissue reaches maximal development at 18 months to 3 years of age (Iwanow, 1930; Coupland, 1954), after which it becomes inconspicuous as a result of either cellular infiltration and fibrosis (Iwanow, 1930, 1932), or dispersion with elongation in a craniocaudal direction, as a result of differential growth (Coupland, 1954). The organs of Zuckerkandl disintegrate during later childhood and no longer form discrete bodies after the age of 7 years, but small collections of chromaffin cells persist in the neighbourhood of the abdominal aorta in the adult and, together with the remains of other para-aortic chromaffin bodies, may be responsible for the development of extra-adrenal phæochromocytomata.

MacKeith (1944) described 165 phæochromocytomata of which 152 arose from the adrenal medulla and 13 from the retroperitoneal tissues between the kidneys, presumably from the paraganglia or organs of Zuckerkandl. Richardson, Ross, and Turnbull (1955) described how both suprarenals were exposed in a man aged 20 suffering from persistent hypertension, but no tumour was found. Later the abdomen was opened and a phæochromocytoma was found in the angle between the left renal vein and aorta.

Phæochromocytomata may contain active functioning cells, rich in pressor amines which stain a deep brown with chrome salts and cause either typical or often bizarre attacks of hypertension or persistent hypertension. Other phæochromocytomata which are relatively poor in pressor amines give only a slightly positive chromaffin reaction and do not affect the blood-pressure. These are usually inert, causing symptoms by local pressure, as in the patient we are about to describe.

The phæochromocytomata of the adrenal medullæ and the phæochromocytomata of the para-aortic bodies, often called 'paragangliomata', are usually well encapsulated and benign, but malignant forms do occur. Davis, Peart, and van't Hoff (1955) reported a case in which paroxysmal hypertension persisted after removal of a phæochromocytoma of the right adrenal. The abdomen was opened, but no other tumour could be found. The patient died. Post-mortem examination revealed many secondary deposits of phæochromocytoma in the ribs, sternum, skull, liver, lungs, and pleuræ. The primary tumour had been considered benign on histological examination, but the secondary deposits, found later, had

similar histological appearances to those of the original tumour and the secondary deposits were found to contain noradrenaline.

Our patient had a non-functioning innocent phæochromocytoma (or 'paraganglioma') which may have arisen from the paraganglia of the pre-aortic plexus or the remains of the organ of Zuckerkandl.

FIG. 319.—Tumour of the organ of Zuckerkandl showing its position in relation to the right kidney, suprarenal, and inferior vena cava.

The tumour caused pain resembling renal colic, presumably due to pressure upon the right renal pedicle.

CASE REPORT

J. R., a man aged 22 years, a 'motor degreaser', was admitted to hospital complaining of pain in the right side of the abdomen which had been present for two days. Nine days before admission he had had a similar attack of pain. The pain had come on suddenly while he was playing billiards and leaning over the table. It gradually increased in severity. At first the pain was like colic, but after an hour or two it subsided and became a constant ache in the right side. He had vomited during the early bouts of pain, and following this he had nausea and did not want food during the next two days. There were no urinary symptoms and his bowels had moved normally.

ON EXAMINATION.—Temperature was 96° F.; pulse, 72/min.; respiration, 20/min.; blood-pressure, 120/90.

He appeared to be in severe pain and lay on his right side with his knees drawn up towards his head.

There was diffuse tenderness over the right side of the abdomen and loin. Rectal examination was negative. Other investigations: Urine, trace of albumin and a reducing substance; neutral; specific gravity, 1020. No abnormal cells or organisms were seen on microscopy.

Plain radiograph of urinary tract showed renal outlines normal. No opaque calculus seen.

Fasting blood-sugar was 80 mg. per cent.

The pain persisted for about eight hours whilst the patient was under observation. In view of this and the negative urinary investigations, a retrocæcal appendicitis was considered to be a likely cause of the pain and operation was advised.

FIRST OPERATION (G. W., Oct. 22, 1956).—The abdomen was opened through a gridiron incision. A normal appendix was found and removed. On further exploration of the abdomen a firm swelling was felt in the retroperitoneal tissues behind the second part of the duodenum and in front of the right kidney. The gridiron wound was closed and the abdomen was opened again more widely through a right paramedian incision. After dividing the peritoneum lateral to the second part of the duodenum, the swelling was found to be lying above the

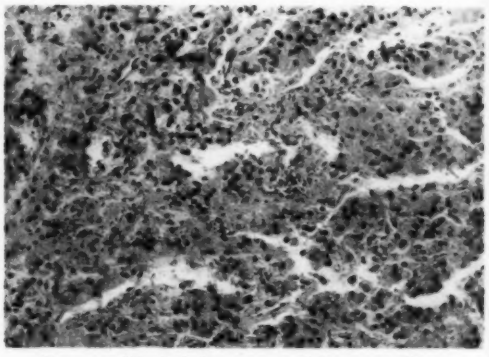

FIG. 320.—Histological appearance of the paraganglioma. (× 75.)

pedicle of the right kidney and below the right suprarenal. It seemed to be about 2 in. in diameter, firm, lobulated, and well-defined. The tumour extended behind the inferior vena cava and right renal vein (*Fig.* 319). A biopsy was done, the peritoneum lateral to the duodenum was sutured, and the abdomen closed.

HISTOLOGICAL REPORT (Dr. T. W. Sutherland, Oct. 29, 1956).—"This small biopsy shows tumour tissue. It is formed of small masses of cells which are generally of somewhat lepidic aspect and are set in a vascular stroma. The cells tend to have a fairly abundant, slightly granular cytoplasm and show some variation in size and shape. The nuclei are usually small, but there is variation in size and some are quite large. They tend to be rather hyperchromatic, although mitoses are infrequent. The appearances suggest that this is a non-specific paraganglioma or chemodectoma." (*Fig.* 320.)

FURTHER INVESTIGATIONS.—Intravenous pyelogram (Oct. 29, 1956): "The renal outlines appear normal. No unusual masses seen in the abdomen. The pyelograms are normal on both sides and there is no evidence of distortion of the pyelograms by external pressure. The bladder is normal."

Radiography of chest and skull showed no abnormality (Nov. 1, 1956).

Hæmoglobin was 106 per cent (Eel colorimeter); white-cell count, 10,600/c.mm.; monocytes, 3 per cent; polymorph neutrophils, 68 per cent; eosinophils, 1 per cent; lymphocytes, 28 per cent.

SECOND OPERATION (M. C. O. and G. W., Nov. 9, 1956).—The 12th rib on the right side was resected and the right adrenal was defined by a retroperitoneal approach after the right kidney had been displaced downwards. The adrenal was normal, but a firm, ill-defined tumour was found internal to it. The tumour was adherent to the right renal vein and extended behind the inferior vena cava, to which it was also closely adherent. The tumour was removed with a segment of the inferior vena cava and the right renal vein. After inserting a large pack and pressing upon it, a clamp was applied to the inferior

vena cava to occlude part of its lumen. The rent in the inferior vena cava was sutured and the right kidney removed. The wound was closed with a drainage-tube in the right kidney pouch.

The patient was severely shocked, but recovered after transfusion.

HISTOLOGICAL REPORT (Nov. 26, 1956).—"A central necrotic area is enclosed by a thin rim of polyhedral cells which vary considerably in size and shape. The nuclei are dense and hyperchromatic. Some granules of brownish pigment are present in the sections which have been treated with chrome solution. A dense connective tissue capsule circumscribes the tumour. Histologically this specimen appears to be a paraganglioma."

Convalescence was complicated by a right pneumothorax, presumably due to injury of the right pleura at the time of operation. A course of dindevan, controlled by prothrombin estimations, was given to prevent thrombosis of the inferior vena cava. After the wound had healed, the patient went home on Dec. 7, 1956.

He was seen periodically as an out-patient. On the last occasion (May, 1957) he had returned to work and was free from symptoms. His blood-pressure was 130 systolic, 75 diastolic.

SUMMARY

A case report is given of a non-functioning extra-adrenal phæochromocytoma, or paraganglioma, occurring in a man aged 22, who complained of severe pain resembling right renal colic, associated with nausea, vomiting, but normal blood-pressure. It is presumed that the tumour caused symptoms by pressure upon the renal pedicle. The tumour was removed. It was simple on histology, but was adherent, probably by inflammatory reaction, to the inferior vena cava and right renal vein which were injured at operation.

We are indebted to Dr. R. E. Coupland for much valuable advice and for permission to make drawings from his photographs for the illustrations for *Fig.* 318.

We are grateful to Dr. W. Goldie and Dr. T. W. Sutherland for advice on the pathology.

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A CASE OF EMBRYONIC SARCOMA OF THE BLADDER IN AN INFANT

BY B. L. WHITAKER, ROMFORD

APPROXIMATELY one hundred vesical tumours of embryonic sarcoma type have now been reported, probably the earliest description being that given by Matthew Baillie (1799) of a specimen which is still to be seen in the Hunterian Collection of the Royal College of Surgeons. In the reported cases there has so far been a slight preponderance of males. The patient is generally under 5 years of age, but cases have been reported in adult life and even in old age. Most of the children have presented with disturbance of micturition, such as dysuria, hæmaturia, or, as in this case, with acute retention. In girls the tumour has, in a high proportion of cases, prolapsed down the urethra to present at the vulva.

The rarity of these tumours has resulted in a scattered series of individual cases with a bewildering nomenclature. They have been described as myxoma, myxosarcoma, fibrosarcoma, rhabdomyosarcoma, botryoid sarcoma, embryonic sarcoma.

It has become evident, however, as more and more cases have been reported, that they form a homogenous group, and are identical with a group of tumours arising in other sites associated embryologically with the mesonephric ducts; for instance, the vagina (100 cases), the prostate, and very rarely, the spermatic cord and the epididymis. The tumours themselves are translucent grape-like masses, often arising by narrow stalks, and displaying a gelatinous appearance of the cut surface.

Irrespective of site they consist essentially of an embryonic mesenchyme, which varies from case to case only in the degree of differentiation. For this reason White (1952, 1955) has suggested that the term "embryonic sarcoma" originally used by Albarran (1892) should be employed to describe the whole group. Microscopically, the bladder tumours are covered by intact transitional epithelium, except where ulceration has taken place as a result of infection.

The tumour cells are small, round, or ovoid, with scanty cytoplasm, and lie in an abundant clear ground substance, which may be slightly basophilic and which contains many reticulin fibrils. Frequently rhabdomyoblasts are present, and cross striations may be seen, especially in sections prepared with Mallory's phosphotungstic acid stain. With hæmatoxylin and eosin staining these cells have strongly eosinophilic cytoplasm with large vesicular nuclei and eosinophilic nucleoli. Mitoses may be present, but are not invariable, and frequently the malignant nature of the tumours is not at first appreciated.

In untreated cases death is usual in under one year. Local removal is generally followed by recurrence, which is often so alarming in its rapidity and extent as to give the first indication of the malignancy of the lesion.

This melancholy sequel is not, however, invariable. Ramey, Ashburn, Grabstald, and Haines (1953)

reported one case alive after twelve years, and White (1955) quotes survivals of fourteen and twenty-two years in two cases of the Great Ormond Street series.

The likelihood of such prolonged survival is small, however, and in recent years the trend has been towards total cystectomy with ureterocolic anastomosis or cutaneous ureterostomy. The number of recorded cases in which recurrence has occurred in the prostate or other portions of the mesonephric 'field' makes it advisable to remove also the prostate and seminal vesicles in the male, and the urethra, vagina, and vestibule in the female.

Such extensive procedures have not been in general use for a sufficient length of time for many long-term cures to be reported, but Flocks and Culps (1955) report one case surviving eight years after pelvic evisceration, and reports of cases still living after four or more years are becoming fairly frequent.

FIG. 321.—The excised bladder and prostate from behind. The posterior wall of the bladder has been cut away and wires inserted in the ends of the ureters. The tumour is seen protruding forwards through the cystostomy opening in the anterior wall.

FIG. 323.—A primitive muscle-cell showing longitudinal and transverse striations. Mallory's phosphotungstic acid. (× 1250.)

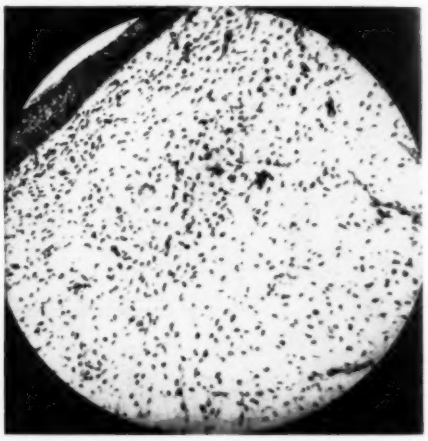

FIG. 322.—A portion of the tumour showing cells lying scattered in the characteristic ground-substance. A portion of the intact transitional epithelium is seen covering the tumour tissue. (× 75.) H. and E.

CASE REPORT

Christopher P., aged 9 months, was admitted on Dec. 12, 1956, with a history of hæmaturia.

His mother's pregnancy had been uncomplicated, although she had been radiographed immediately before delivery. The child's birth-weight was 8 lb. 15 oz. At birth he was noted to have a lumbar meningocele. This was excised at the age of 7 weeks (Mr. J. Thompson Fathi) with an excellent result.

There were no significant illnesses in the mother's medical history, but the father had been investigated for hæmaturia in 1950, and found to have bilateral hydronephrosis of uncertain aetiology.

The child had been in good health until Nov 27, 1956, when his parents noticed that the napkin was stained with bloody urine. Five days later there was further bleeding which subsided fairly rapidly. On the evening of admission there was a further brisk bleed and the child appeared to be in pain. On admission his temperature was found to be 101° F. The cardiovascular and respiratory systems were normal, pulse 140, respirations 28.

Examination of the back showed a transverse scar 8 cm. in length over the lower lumbar spine. The central nervous system was normal.

Palpation of the abdomen revealed the presence of a hard fusiform mass arising out of the pelvis to the level of the umbilicus. On rectal examination this mass was felt to compress the rectum and appeared to be due to a distended bladder. The prostate was normal for the child's age, scrotum and testes were normal, and the penis was normal apart from a slight balanitis. The prepuce did not constitute a barrier to the passage of urine. A catheter was passed and 150 ml. of urine withdrawn, following which the suprapubic mass had disappeared. The catheter was withdrawn in the hope that

normal micturition would be re-established but retention quickly returned and was associated with the passage of several pieces of fleshy material per urethram.

Examination of the urine withdrawn showed it to be sterile, heavily blood-stained, acid, and to contain 1·1 g. per cent of protein. The blood-urea was estimated and found to be 51 mg. per cent.

On Dec. 17 a suprapubic cystostomy was performed under general anæsthesia. The bladder wall appeared thickened and rather pale. On opening the bladder a slightly lobulated grape-like tumour was disclosed, posterolateral to the left ureteric orifice, and attached to the bladder wall by a narrow pedicle. This tumour was excised and the base diathermized. A De Pezzer catheter was inserted and the wound closed.

Microscopy of the excised tumour was performed, the report being as follows: "A juvenile type of fibrous connective tissue in which intercellular substance is colourless or yellow in V.G. preparation. Very cellular with a good many mitoses. Conclusions: a fibrous connective tissue tumour with potentialities for recurrence."

This conclusion was unfortunately rapidly demonstrated to be correct, for on Feb. 4, 1957, that is, 47 days after the first operation, a piece of tumour larger than the original was spontaneously extruded from the cystostomy opening.

The opinion of Dr. Leslie White of Great Ormond Street was sought as to the nature of the tumour, and he confirmed the view of our own pathologist that this was an example of an embryonic sarcoma.

An intravenous pyelogram performed on Dec. 21, 1956, had shown both kidneys to concentrate the dye well, and the right kidney appeared normal. On the left, however, hydronephrosis was present. The bladder outline was extremely irregular. No evidence of secondary deposits was found on radiography of the skull, pelvis, spine, or chest.

Accordingly, bowel sterilization with chloramphenicol 125 mg. 6-hourly was begun, and on Feb. 11, 1957, total cystectomy and bilateral ureterocolic anastomosis was undertaken as a one-stage procedure via a midline suprapubic incision. No local metastases were observed at operation, and the tumour appeared to be confined to the bladder, but both ureters were noted to be considerably dilated.

The distal point of section was made as low as possible, but subsequent examination of the excised specimen revealed that a small portion of the apex of the prostate had been left behind.

Considering the magnitude of the procedure the patient's recovery was surprisingly rapid. Transfusion of 200 ml. of blood was necessary during operation and again the following day. Chloramphenicol was continued for 4 days and then replaced by penicillin 100,000 units 6-hourly.

Serum electrolyte estimations on Feb. 16, 1957, were as follows: Sodium 130 mEq./l.; potassium 5 mEq./l.; chloride 111 mEq./l.; CO_2 combining power 16 mEq./l.; blood-urea 42 mg. per cent.

On March 25 radiotherapy was begun to a total dosage of 1500 r via anterior and posterior fields of 10 × 10 cm. using 250 kV. and one copper and one aluminium filter. This treatment was followed by a moderate skin reaction.

The child was eventually discharged home 81 days after the cystectomy, apparently in good health. As yet there has been no sign of local recurrence, but there is some degree of impairment of renal function together with a tendency to hyperchloræmic acidosis as shown by the following electrolyte estimations performed on July 2, 1957: Plasma CO_2 combining power 8·5 mEq./l.; serum chloride 120 mEq./l.; serum sodium 141 mEq./l.; serum potassium 4·85 mEq./l.; blood-urea 54 mg. per cent.

Unfortunately it has not proved practicable to perform serial electrolyte estimations owing to the difficulty of venepuncture.

PATHOLOGY.—*Fig.* 321 shows the bladder and prostate from behind, with the posterior part of the bladder wall removed. The lower half of the bladder cavity is filled with growth which appears to arise from the trigone and anterior wall and to be protruding through the cystostomy opening. Both ureteric orifices are involved in tumour.

Histologically the tumour was identical with the biopsy specimen described. *Fig.* 322 shows a low-power view of a portion of tumour which is covered by intact transitional epithelium. The tumour cells are widely dispersed and surrounded by colourless ground-substance. Scattered here and there throughout the tumours are large cells with deeply eosinophilic cytoplasm. Sections stained with phosphotungstic acid show numerous strap-like cells with well-marked cross striations. These rhabdomyoblasts are illustrated in *Fig.* 323.

SUMMARY

The natural history and pathology of embryonic sarcoma of the bladder are briefly reviewed.

A case of embryonic sarcoma of the bladder in an infant, presenting as acute retention, is described.

Acknowledgements.—I should like to express my thanks to Mr. F. N. Foster for his encouragement and advice and for permission to publish this case. Also to Dr. Leslie White who made available to me a great deal of information and data, to Dr. E. A. Atkinson for his help in the interpretation of the histology, to Mr. E. A. Sheppard of the Department of Medical Photography, Oldchurch Hospital, for the photograph of the bladder, to Mr. S. Hogwood of King's College, London, for the photomicrographs, and to Professor T. Nicol for kindly permitting me to use the photographic facilities of his department.

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VOLVULUS OF THE SPLENIC FLEXURE

REPORT OF A CASE WITH A REVIEW OF THE LITERATURE

By N. A. BLUMBERG

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VOLVULUS of the splenic flexure is an extremely rare condition, not even mentioned in standard works on surgery and pathology. At the time that the case described here was under treatment and this paper was begun, only three such cases could be traced. Before this paper was complete, a further two reports were available. This case is presented primarily because of its rarity. However, Buenger (1954) reports a case which was easily reduced by a barium enema and he suggests that the condition may occur more frequently than is supposed. He suggests that a partial volvulus of the splenic flexure could account for the chronic bloating, constipation, and gurgling which is frequently encountered in patients in whom no abnormality is demonstrated.

CASE REPORT

P. W. P., a retired police officer, aged 67, was admitted to the Ipswich and East Suffolk Hospital on Oct. 10, 1956. It was impossible to obtain a coherent history from him, because of marked dementia. He admitted to having had occasional griping abdominal pains, but did not think that there had been any such pain on the day of admission. As far as one could assess, his bowel habit was normal and he thought that there had been an action on the day of admission. There had been no vomiting. He was incapable of producing any other pertinent information, and being paranoid, strongly resented any form of questioning.

Several years previously he had had a right inguinal herniorrhaphy. Following this he developed retention of urine. A suprapubic cystostomy was done, followed later by a prostatectomy. He subsequently developed an incisional hernia in the prostatectomy scar and was fitted with a belt. There was also a story of appendicitis.

ON EXAMINATION.—This showed a man of healthy appearance, who looked younger than his age, in no obvious distress or pain. The tongue was slightly furred. There was a lattice of abdominal scars and a moderate sized easily reducible hernia in the subumbilical midline scar. There was generalized abdominal distension, more marked in the flanks. There was no tenderness and no abdominal masses were palpable. No bowel sounds were heard. Rectal examination revealed no abnormality apart from an empty rectum. There was no blood on the examining finger.

Plain X-ray of the abdomen in both erect and recumbent positions showed multiple fluid levels in both small and large bowel, and gross gaseous distension in the large bowel. Two enemata produced no result.

AT OPERATION.—A lower right paramedian incision was employed which extended partly into the incisional hernia. There was enormous distension involving the entire large bowel, which was paper thin. The last 15 in. of ileum were considerably dilated. Exploration was difficult because of the distension and had to be conducted with the utmost gentleness, for fear of rupturing the bowel. It revealed no obvious cause for the obstruction. The incisional hernia was empty. There was a dense mass of adhesions and omentum in the right iliac fossa, presumably from a previous appendicectomy, anchoring the cæcum. These were divided to mobilize the cæcum. A small pouch of cæcum was then exteriorized through a short incision and a Malecot catheter inserted into it.

POST-OPERATIVE PROGRESS.—The cæcostomy drained well and the abdominal distension decreased slowly, but not completely. Blood biochemical studies on October 13 showed normal values for hæmoglobin, serum potassium and sodium, chlorides and alkali reserve, but the urea level was raised to 50 mg. per cent.

Six days after operation (Oct. 16) a sigmoidoscopy was performed without anæsthesia. The instrument was passed to 20 cm. and no abnormality was detected. However, the procedure precipitated an acute mania and the patient became unmanageable, necessitating his transfer to a mental institution. After ten days he returned to the surgical ward, now quiet, with a very distended abdomen, although the cæcostomy was draining adequately. A barium enema was performed on Oct. 30. It showed a "volvulus of the left colon" (*Fig.* 324).

FIG. 324.—Barium enema showing the typical spiral pattern of the mucosal folds alternating with bands of increased radiance, indicating a volvulus with incomplete obstruction.

SECOND OPERATION.—On Oct. 31 a laparotomy was performed through a left paramedian incision. The generalized distension found at the first operation had largely subsided, but the transverse colon was grossly dilated and on a long mesocolon. An enormous volvulus, some four feet long, involving the splenic flexure, was delivered with difficulty from the left subphrenic area and unwound. The flexure was suspended on a long mesentery and there was complete absence of the phrenicocolic ligament.

The mesentery was divided between clamps, the loop double-barrelled for a short distance, and the affected segment resected between Payrs clamps (*Fig.* 325). The stump was exteriorized through the upper end of the main incision. In the mesocolon immediately adjacent to the hepatic flexure was a hard irregular mass the size of a golf-ball. There appeared to be involvement of adjacent lymph-nodes. This mass could not be satisfactorily examined through the exposure, but there

appeared to be no continuity with the related bowel, which appeared normal. Before the patient left the operating table, he had a bowel action.

POST-OPERATIVE PROGRESS.—The patient had frequent bowel actions through the rectum. The proximal clamp was removed after 24 hours and the colostomy acted well. The clamp on the distal segment was left to separate spontaneously. The abdominal distension soon disappeared, and the patient made a rapid recovery; his mental condition improved noticeably and he became quite amiable, even recognizing his medical attendants.

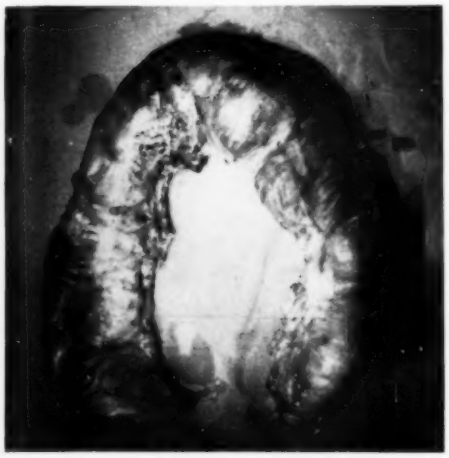

FIG. 325.—The resected splenic volvulus.

THIRD OPERATION.—On Dec. 4 the colostomy was closed. This was done in two layers, after freeing some adherent small bowel. The abdominal wall was closed in layers.

POST-OPERATIVE PROGRESS.—The cæcostomy continued to discharge for almost two weeks but rapidly became smaller and by Dec. 17 had closed. When seen at the follow-up clinic on Jan. 16, 1957, the patient was well, with no discharge from the cæcostomy.

DISCUSSION

Six reported cases of volvulus of the splenic flexure have been found in the literature. Buenger (1954) reported 2 cases. In each case there was a story of irregular bowel habits; the first patient (aged 78) had episodes of constipation and diarrhœa, and the second (aged 53) had a history of constipation. Buenger found tenderness in the left upper quadrant in one case. The first case was due to adhesions and a thick band which extended from the abdominal wall to the transverse colon, enveloping the splenic flexure. In his second case the volvulus could be easily reduced by a barium enema. This patient had a history of low backache with a drawing sensation radiating down her legs during periods of constipation. The lesion was detected during a routine barium enema in the investigation of the patient's hæmorrhoids.

Young (1955) described a case of coexistent volvulus of the splenic flexure and cæcum in a patient aged 19. The splenic volvulus was occasioned by peritoneal bands which were congenital. These extended from the splenic flexure to the left side of the diaphragm. He resected the loop and performed an end-to-end anastomosis.

Wolf and Guglielmo (1956) reported a case of splenic flexure volvulus with complete obstruction in a woman aged 58. They found diffuse abdominal tenderness and rebound tenderness. Their patient refused operation. Under conservative treatment the volvulus corrected itself. This patient had had a gastrectomy eleven years previously and she probably had adhesions in the area.

Poppel, Zeitel, and Abrams (1956) reported 2 cases of splenic flexure volvulus. The first patient was aged 63 and had undergone previous abdominal surgery. The volvulus was demonstrated by a barium enema. At operation there was agenesis of the greater omentum and phrenico-colic ligament, and redundancy of the flexure. The second patient was aged 70. He had a history of chronic constipation and previous abdominal surgery. At operation there was a short splenic mesocolon and an inflammatory stricture in the sigmoid colon, producing chronic obstruction. In each case the volvulus was resected and continuity restored by end-to-end anastomosis. Microscopic examination of both operation specimens revealed no abnormality in the intramural nerve plexuses.

The radiographic findings in splenic flexure volvulus are identical to those of volvulus of the sigmoid. An admirable description of these is provided by Ritvo and Golden (1946). They point out that plain films are unreliable in determining the site of obstruction. By demonstrating markedly distended loops and, in addition, fluid levels in cases where there is a closed loop, they indicate only that obstruction is present, but do not determine the exact site. If there is complete obstruction, enema fluid cannot flow into the loop and only the bowel below the site of obstruction will fill. At this site there will be a point of stenosis which is smooth, sharply defined, and either rounded or tapered. If obstruction is incomplete and some of the contrast medium passes through the narrowed points, spiral bands of linear density, alternating with areas of increased radiance, delineate the torsion. Under screening it is possible to demonstrate the corkscrew-like arrangement of the mucosa. After the examination they recommend further films after the expulsion of the barium, to show the volvulus more clearly.

The literature shows that volvulus of the colon, not in the sigmoid, is always associated with a congenital abnormality or an acquired defect. Martin and Ward (1944) reported a case of megacolon associated with volvulus of the transverse colon. The bowel cannot undergo torsion where it is fixed to the posterior abdominal wall. It must have the mobility which a mesentery provides before it can undergo axial rotation.

Wilson, Desforges, Dunphy, and Campbell (1954) reported 8 cases of cæcal volvulus. In these, 4 had undergone previous abdominal surgery. They found that constipation was an important factor. Abdominal tenderness was absent or present, depending on the stage of the disease. In the present case one cannot correlate the presence of a mass in the region of the hepatic flexure with the appearance of a volvulus several inches distal to it.

The volvulus in this case was clearly due to the persistent splenic mesocolon, with mobility of the redundant loop. Although the patient presented a multitude of intraperitoneal adhesions, there were none in the vicinity of the splenic flexure and there were none involving the left colon. One cannot see how the adhesions in this patient were in any way responsible for the development of the volvulus. A history of constipation was not obtained.

The barium enema shows the typical picture of a volvulus with incomplete obstruction. The plain films were unreliable in showing the site of obstruction. It was not possible to differentiate between the closed loop of the volvulus and the second loop, constituted by the length of proximal intestine. The quality of these films is too poor for reproduction. Unlike the picture which occurs with volvulus of the sigmoid or cæcum, the volvulus, as was shown at operation, remained in its own habitat in the left subphrenic area.

The initial improvement following cæcostomy was due to decompression on the proximal loop, which probably secondarily eased the degree of tension at the neck of the volvulus.

CONCLUSIONS

Splenic flexure volvulus is extremely rare. The case of reduction in two reported cases suggests that it may occur more commonly than is supposed. The majority of reported cases have occurred in the older age-groups.

It occurs where there is a redundant loop on a persistent mesocolon and is predisposed to by the presence of adhesions, congenital or acquired, in the neighbourhood of the flexure.

Constipation is an important aetiological factor.

It may be secondary to obstruction in the distal colon from any cause.

Local abdominal tenderness may be present but its absence is of no significance.

Plain radiographs of the abdomen are of limited value and a barium enema is necessary to localize the disease.

SUMMARY

A case of volvulus of the splenic flexure with resection by the Paul-Mikulicz method is reported, and the literature is reviewed. I believe it to be the seventh case described and the fourth to be successfully resected.

Acknowledgements.—My thanks are due to Mr. P. B. Counsell, under whose care the patient was admitted and who performed the second and third operations, for permission to publish this case.

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DUODENAL OBSTRUCTION DUE TO RUPTURE OF AORTIC ANEURYSM

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DUODENAL obstruction caused by an unruptured aortic aneurysm has been reported by Washburn and Wilbur (1936), Blakemore (1947), and Dunning and Jones (1950). A case of duodenal obstruction due to rupture of an aneurysm of the abdominal aorta is now presented.

CASE REPORT

W. S., a man of 69 years, was admitted to St. Luke's Hospital, Bradford, on Nov. 10, 1956, with a history of effortless vomiting of bile-stained fluid during the last two days. During the previous two weeks he had experienced anorexia and also epigastric discomfort, most marked half an hour after food. There was no past history of abdominal symptoms, but he had suffered from bronchitis and angina of effort for nearly five years.

ON EXAMINATION.—He was dehydrated and his general condition was poor. The heart-sounds were normal and the blood-pressure was 110/80. A large swelling showing expansile pulsation was present in the upper abdomen. A soft systolic murmur was audible over the swelling. There was no abdominal tenderness or muscular rigidity and both femoral pulses were present. The remainder of the physical examination revealed the signs of chronic bronchitis.

Investigations.—Hæmoglobin, 70 per cent (11·2 g.); blood-urea, 105 mg. per cent; Wassermann, negative; plain radiograph of abdomen (Dr. P. P. Franklyn): "There is a soft tissue mass to the left of the mid-abdomen with scattered areas of calcification in it".

A provisional diagnosis of duodenal obstruction probably due to aortic aneurysm was made. Treatment to restore the fluid and electrolyte loss was instituted. Vomiting ceased after the day of admission and the patient was able to retain oral fluids. On Nov. 14 the blood-urea was 55 mg. per cent and the serum electrolytes were normal, but his general condition remained poor. On Nov. 15 gastric peristalsis was visible and a stomach splash was elicited, but he did not vomit. His condition deteriorated rapidly and he died on Nov. 16.

POST-MORTEM EXAMINATION.—There is extensive atheroma of the entire aorta, iliac and coronary arteries. A saccular aneurysm of the aorta is present between the

origins of the renal arteries and the inferior mesenteric artery. This aneurysm is bulging forwards and has a dense fibrous wall lined by a thin layer of ante-mortem thrombus. A calcified atheromatous plaque is present in the lower part of the aneurysm wall. Rupture has occurred at this site forming a retroperitoneal hæmatoma, firm at the periphery and semi-fluid at the centre. The

FIG. 326.—Sagittal section through aneurysm, showing the forward displacement of the duodenum and pancreas by the hæmatoma. The duodenal lumen at X is reduced to a narrow slit.

pancreas and the duodenum have been displaced forwards by this hæmatoma and the lumen of the third part of the duodenum reduced to a narrow slit (*Fig.* 326). The stomach and duodenum proximal to this obstruction are dilated and contain about 30 oz. of bile-stained fluid. Distal to the obstruction the posterior duodenal wall is atrophic and here about 10 oz. of blood from the hæmatoma have burst through into the lumen.

The aortic arch and the aortic valves show no evidence of syphilis. The remainder of the autopsy reveals no significant findings. Histological examination of multiple sections from the aorta and aneurysm wall show only atheromatous change. Early organization is present at the edges of the hæmatoma.

DISCUSSION

The histological appearance of the hæmatoma suggests that the initial rupture of the aneurysm occurred about one week before death, coinciding with the time of onset of symptoms of obstruction. The remission of obstructive symptoms could be explained by the temporary cessation of the initial leakage. Further bleeding appears to have taken place just before death, causing the return of duodenal obstruction. The terminal event was rupture of the hæmatoma into the duodenal lumen.

The final duodenal obstruction seems to have been a mechanical one, as pressure from the hæmatoma has reduced the lumen to a narrow slit. However, it is possible that ileus was a factor in the earlier episode of obstruction. Paralytic ileus occurred in 19 out of 20 cases of retroperitoneal rupture reported by Zech and Merendino (1954).

A feature of this case was the absence of severe pain throughout the entire course of the illness and particularly at the time of rupture of the aneurysm. Acute pain is a common symptom of rupture or impending rupture of abdominal aneurysms (Blakemore, 1947; Zech and Merendino, 1954; and King and Robinson, 1956). The present patient only experienced mild epigastric discomfort and the diagnosis of rupture was not made before death.

SUMMARY

Obstruction of the duodenum due to rupture of an aneurysm of the abdominal aorta is described. The duodenal lumen was almost completely occluded by pressure of the hæmatoma.

An interesting feature was the absence of severe pain at the time of rupture.

Acknowledgements.—We are grateful to Dr. J. A. Price for permission to publish this case; also to Mr. E. F. Hill for technical assistance and to Mr. P. Harrison for the photograph.

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REVIEWS AND NOTICES OF BOOKS

Reconstructive and Reparative Surgery. By HANS MAY, M.D., F.A.C.S., Associate Professor of Surgery, Graduate School of Medicine, University of Pennsylvania. Second edition. 10×6¼ in. Pp. 1115+xviii, with 1030 illustrations, 55 in colour. 1958. Philadelphia: F. A. Davis and Co. 225s.

THERE can be little doubt that plastic surgery has come into its own, and the cause of this is the experience gained in two world wars. Ten years have elapsed since the publication of the first edition of this large and comprehensive work on reconstructive and reparative surgery. Although this 10-year interval is a relatively short span of time, yet rapid and profound changes have taken place. The plastic surgeon of to-day has a very large field, and this field is increasing.

We are experiencing a phase of ultra-specialization which is not good for the surgical profession as a whole. This work includes a vast field, in which plastic repair to all the tissues of the body is included. The use of various methods of skin-grafting is described in detail, and this section is well illustrated. The treatment of burns is admirably dealt with.

Various methods of treatment in nerve injuries are well set out. Perhaps the best section of the book is that devoted to the treatment of injuries of the hand, which could not be bettered.

The author has had the right background, for having graduated from the University of Freiburg, he studied pathology under Ludwig Ashoff—surely the best experience a surgeon could have.

This book should prove a practical guide to all surgeons who wish to practise reconstructive and reparative surgery.

An Introduction to Surgery. Edited by D. H. PATEY, L.R.C.P., M.R.C.S., F.R.C.S., Director of Surgical Studies, Middlesex Hospital. Second edition. Pp. 228+xii, with 54 illustrations. 1958. London: Lloyd Luke. Cloth bound, 17s. 6d.; paper-covered, 9s. 6d.

ELEMENTARY instruction in surgical principles is one of the most difficult duties that a teacher has to perform. Sometimes this is left entirely to junior men, but there is no doubt that this type of instruction is far better given by men of experience who have learnt, after years of contact with students both in the wards and in the examination hall, what it is that they find difficult to understand or to remember.

The distinguished panel of authors who have helped to write this book ensures that it covers the field in a way which is easy to understand, and that the student will be able to remember the basic principles of clinical surgery which are so ably described.

Based on the surgical part of the introductory course given at the Middlesex Hospital, there are three main sections: the first deals with general principles, the second with methods of examination, and the third with practical procedures. At the end of the book there is a most useful glossary of 'Operation and Clinical and Pathological Terminations', such as '-ectomy', '-ostomy', '-oma', '-ectasis', and so on, which the student at first finds so confusing, together with common surgical terms. An appendix gives normal values of the constituents of plasma, blood, urine, and other body substances.

The book has been published in two forms: one with a stiff cover for the library, and the other, at a most moderate price, with a paper cover for the student's pocket. It might confidently be anticipated that it will be the latter edition which will be in the greatest demand. This is a book which should be in the possession, indeed in the pocket, of every student just entering the surgical wards. It will show him the way around and help to allay that sense of bewilderment which so often assails him at this stage.

As this book will undoubtedly go into many editions, it would not be the part of an entirely friendly critic to fail to mention a few points which might be improved. Thus, in the inset drawing of a subdural hæmatoma it is very difficult to make out the various layers, and vomiting is not mentioned as a symptom of intracranial hæmorrhage. It would have been better to have taken a cyst of the epididymis as an example of translucency rather than a hydrocele which may require elaborate manipulation with blankets and other darkening devices to reveal this sign.

Later on, in describing tapping a hydrocele, it is stated that "an injection of local anæsthetic *may* be made into the skin of the scrotum" before inserting the trocar. "May" should surely be replaced by "must".

The authors, and particularly the editor, are to be congratulated on producing a fine contribution to surgical teaching and one that reflects the greatest credit on their hospital.

Pathophysiologische Grundlagen der Chirurgie in ihrer Auswirkung auf chirurgisches Handeln. By TH. OTTO LINDENSCHMIDT, Hamburg. 9½×6¾ in. Pp. 410+xx, with 39 illustrations. 1958. Stuttgart: Georg Thieme. D.M. 56.

No modern text on applied physiology has been published in the German language since 1945. The author has tried to bridge the intervening gap by writing a short textbook with the twofold purpose of supplying the practising surgeon with a concise practical guide, and also of presenting critically the present state of our knowledge to those engaged in scientific research.

The outcome calls for comparison with Samuel Wright's evergreen *Applied Physiology*, and it can be said that understandably the high standard of the latter has not been reached. The section on body-fluids, for instance, is certainly less extensive and far less personal. The very scarce use of diagrams makes one wonder if a beginner would really be able to grasp all the essentials. On the other hand, the book as a whole is more orientated towards surgical practice, stressing pre- and post-operative care, and in the section on the gastro-intestinal tract many a useful hint is to be found.

A wise selection seems to have been made in the ample references to recent international literature at the end of each chapter. The book is well printed in clear, modern type, but the price seems unduly high.

Those who have studied a standard text on applied physiology and have a working knowledge of German may spend some useful hours in a library perusing the pages of Mr. Lindenschmidt's book.

Carcinoma of the Lung. Edited by J. R. BIGNALL, M.D., M.R.C.P., Assistant Physician, Brompton Hospital; Senior Lecturer, Institute of Diseases of the Chest, Brompton Hospital; Research Assistant, Radiotherapy Department, Institute of Cancer Research, Royal Cancer Hospital. 9¾×6½ in. Pp. 298+xii, with 62 illustrations. 1958. Edinburgh: E. & S. Livingstone Ltd. 55s.

THIS is the first volume of a new series of monographs dealing with the treatment of cancer in various parts of the body. The general editor of this series is Professor D. W. Smithers, and one cannot think of a better or more capable person to undertake this enormous task.

This first volume is devoted to carcinoma of the lung and it is a most comprehensive work, dealing as it does with every facet of this all-too-frequent form of cancer.

There are five separate and distinct sections in this volume. The first deals with the mortality from cancer of the lungs in England and Wales and contains a vast amount of information concerning the mortality rates in the different age-groups.

Section two is concerned with our present knowledge of the causation of carcinoma of the lung. The question of smoking and atmospheric pollution and the part they play in the causation of carcinoma of the lung is admirably dealt with.

Section three is devoted to the pathology of carcinoma of the lung, and this is a most interesting account of the microscopical anatomy of the disease. An excellent account of the spread of the malignant process is also given.

In section four the clinical course of the disease is portrayed and its various manifestations are described in an interesting and lucid way.

Section five deals with the treatment of carcinoma of the lung, and Mr. W. P. Cleland gives an excellent account of the surgical treatment, while Professor Smithers considers the radiotherapeutic treatment.

There can be no doubt whatever that this admirable monograph will become the standard reference volume on cancer of the lung.

If the future volumes of this series are of the same standard as the present one, then the publishers are to be congratulated on a great work worthy of the best traditions of British medicine.

We look forward with great interest to the publication of further volumes in this series. The price of this book is most reasonable.

The Care of the Patient in Surgery, including Techniques. By EDYTHE LOUISE ALEXANDER, R.N., B.S., M.A., Director of Nursing Service and Principal of the School of Nursing, Lutheran Medical Centre, Brooklyn, N.Y. Third edition. $9\frac{3}{4} \times 6\frac{1}{2}$ in. Pp. 840, with 555 illustrations, including 5 in colour. 1958. London: Henry Kimpton. 95s.

HERE is an American book written for theatre sisters and theatre nurses. Like most American text-books, it is comprehensive, beautifully produced, and rather expensive. It exemplifies, however, the differences in approach to nursing between that country and our own. In America, nursing is a profession of university graduate status; in Britain, nursing is a vocation demanding the necessity for technical training. In Britain, the standard of ward nursing is second to none in the world; in America, the standard of theatre assistance is, on the whole, higher than our own. This is because the American system, demanding a high standard of academic achievement, is better suited to the training of theatre nurses, where the vocational qualities of sympathy with suffering, understanding, and devotion are not quite so constantly in demand. When one studies this book, with its chapters on the planning of an operating theatre, the management of autoclaves, the technical details of instruments, and the care and preparation of suture material, together with an account of the vast amount of knowledge which the competent theatre nurse must acquire, one has a feeling that this branch of the nursing art is a profession, *sui generis*, just as are radiology and physiotherapy, and that a better general standard of performance would be attained if this fact were recognized by those authorities responsible for the recruitment and training of nurses.

No praise can be too high for the way in which the problems confronting the theatre nurse are discussed. The illustrations of instruments and the description of requirements for special operations, including the endoscopies, are excellent. This is a book which should be provided by hospital authorities for all theatre sisters and it would set them a standard which, if achieved, should improve the conduct of operations throughout the country.

Operable Herzleiden. By J. JACOBI, Hamburg; and M. LOEWENECK, Hamburg. $10\frac{1}{4} \times 6\frac{3}{4}$ in. Pp. 175 + viii, with 155 illustrations. 1958. Stuttgart: Georg Thieme. D.M. 49.50.

THIS book concerns itself with cardiovascular lesions amenable to cure or amelioration by surgical means, and embodies recent advances in the realms of diagnosis, assessment, and surgery. Though based in part, it is stated, on the authors' apparently quite extensive personal experience, no attempt is made in it to draw any conclusions therefrom. In order to cover fully the differential diagnosis, some disease entities not yet within the scope of surgery are included.

Diagnosis, prognosis, and the indications for surgical intervention are well discussed, though the interrelationship of the subject with pregnancy, in which some particularly gratifying results have been achieved, is dismissed in five lines. Apart from touching on such practical aspects as pre- and post-operative management, anæsthesia, and the ancillary techniques of hypothermia and extra-corporeal circulation, no attempt is made to go into surgical minutiæ. However, outstanding operative details are summarized in diagram form.

The illustrations are of high quality. The relevant modern literature is liberally drawn upon, with an American bias when foreign sources are being used.

It is difficult to assess the usefulness of a work of this sort, and to resist the impression that it is premature. Those interested in the surgery of the heart and related great vessels, still in the course of development, would probably be better served by reference to source publications.

Lehrbuch der Kinderchirurgie. By MAX GROB, in co-operation with MARGRIT STOCKMANN and MARCEL BETTEX. $10\frac{1}{4} \times 6\frac{3}{4}$ in. Pp. 775 + xii, with 876 illustrations. 1957. Stuttgart: Georg Thieme. D.M.157.

IN the introduction to this text-book of pædiatric surgery, Dr. Grob expresses the opinion that the surgery of infancy and childhood should become a separate specialty and that its department should be housed in a pædiatric rather than in a surgical clinic. His idea of pædiatric surgery is that it is a specialization according to age and not to a certain region or tract, resulting in a certainly fascinating combination of general surgery with the surgical sub-specialties. This synthesis would become possible because the types of affections encountered are in a way limited and determined by the age-groups included. His book therefore comprises general, orthopædic, neurosurgical, thoracic, and urological surgery.

After a general section on pre- and post-operative treatment, also briefly covering anæsthetics, the regional sections deal with surgery of the skull, face, neck, thorax, abdomen, urogenital system, vertebral column, skin, and soft tissues, and finally bones and joints.

The style is clear and easy to read, long and complicated sentences which make some German books very hard to tackle having been avoided.

Surgical pathology has been reduced to the minimum required, but the clinical descriptions, containing some very attractive classifications, are extensive enough to prevent the book from becoming just a manual of operative pædiatric surgery. The discussions of surgical treatment are concise and helpful, stressing techniques that have proved themselves in personal use.

The number of illustrations, supplied by the authors' clinic, is remarkable, totalling up to 876 (761 pages!). Included are photographs in black and white and in colours, diagrams, drawings, and quite a few radiographs. They are of very good quality and greatly facilitate the reading of this book.

There are practically no references to literature, which is the only major criticism that should be mentioned.

New subjects are allotted more space than the more established ones, orthopædics for instance getting only 122 pages, and the same tendency is found in topics which obviously have the authors' special interest, resulting among other things in an admirable discussion of craniosynostosis.

The presented opinions are occasionally rather personal and not always in keeping with what is generally accepted (in the treatment of full-thickness burns no mention is made of primary excision with immediate skin-grafting).

The value of the book is greatly enhanced by the fact that it is based on the authors' very extensive personal experience of twenty-five years' work at the surgical department of the University Children's Clinic at Zürich.

It is an excellent companion to Ladd and Gross's *Surgery of Infancy and Childhood*, and should provide interesting reading not only for surgeons and postgraduate students, but also for obstetricians and pædiatricians.

Ligament and Tendon Relaxation treated by Prolotherapy. By GEORGE STUART HACKETT, M.D., F.A.C.S., Consulting Surgeon, Mercy Hospital, Canton, Ohio. Third edition. 9×5¾ in. Pp. 151+xviii, with 32 illustrations. 1958. Springfield, Ill.: Charles C. Thomas (London: Blackwell Scientific Publications). 51s.

THE fact that a third edition of this book is published is sufficient indication that the author's ideas have attracted attention. The claim is made that he is able to report for the first time in history the most frequent cause of chronic painful skeletal disability and provide a cure by prolotherapy, a treatment aiming at the production of new bone and fibrous tissue cells at ligamentous and tendinous attachments to bone. In this edition the new material deals with pain of the 'sciatica' type, referred from 'relaxation' of ligaments of lumbosacral and sacroiliac joints and disabled tendons of lumbar muscles. Those who are not familiar with Dr. Hackett's work and experience may regard his methods of arriving at a diagnosis, his description of the pathology of ligament lesions, and his methods of treatment as most original, and be inclined to consider he is a pioneer in explaining and curing many aches and pains, which are too often classified in this country as 'rheumatism'.

His theme is that relaxation of a ligament may occur under many conditions, the most evident symptom being pain and the most apparent physical sign a trigger-point tenderness, both of which will disappear after injection of a solution within the relaxed ligament. He names one solution for out-patients and another for those in hospital. The exact method of injection into many parts of the body is described, and 39 cases are quoted, most of them referring to patients with low backache and some with tendon 'relaxation'. Some of the last group had rotator cuff symptoms. Readers will agree that referred pain frequently exists in the type of case quoted, but the author is not convincing in his explanation of the reasons for this referred pain, and little stress is laid on muscle spasm as an important indication of deep-seated lesions. His reference to a well-known surgeon's statistics on backache ceased to be of interest when prolapse of an intervertebral disk became recognized. A number of the author's pathological findings are well established and his observations on the changes in ligaments must arouse interest and deserve investigation. They may be acceptable when practical experience proves their value. Readers will be anxious to find reports on a large number of patients affected by the conditions described and treated on the lines advocated. The arrangement and printing of this volume are of high standard.

Skin Grafting. By JAMES BARRETT BROWN, M.D., Professor of Clinical Surgery, Washington University School of Medicine; and FRANK MCDOWELL, M.D., Associate Professor of Clinical Surgery, Washington University School of Medicine. Third edition. 9¾×6¾ in. Pp. 411+xvi, with 328 illustrations. 1958. London: Pitman Medical Publishing Co. 105s.

THE third edition of this well-known work has been carefully revised and many sections of the book have been rewritten. There are several new sections dealing with the varied uses of the pedicle flap, the permanent pedicle blood-carrying flap, the homograft, and the composite graft.

An excellent chapter on the repairs of the genitalia should convince surgeons that plastic repair and skin grafting succeed in what appear to be hopeless cases of penoscrotal avulsion.

The use of post-mortem homografts is interesting and they appear to give excellent results. When it is considered that living post-mortem homografts can be preserved in a skin bank for a few weeks, it behoves all hospitals to institute such banks in this traumatic age.

The authors have the gift of explaining their various techniques in a very lucid style, and their clinical and operative photographs are outstanding. The coloured plates in this new edition are pre-eminent.

Fractures and Other Injuries. By the members of the Fracture Clinic of the Massachusetts General Hospital and the Faculty of the Harvard Medical School. Edited by EDWIN F. CAVE, M.D. 10×7 in. Pp. 863+xviii, with 612 illustrations. 1958. Chicago: The Year Book Publishers Inc. 210s.

THIS comprehensive work is the outcome of the co-operation of the members of the Fracture Clinic of the Massachusetts General Hospital and of the Faculty of the Harvard Medical School. Some thirty-nine contributors have been employed in the writing of this volume. Every facet of the ever-increasing speciality of traumatic surgery is adequately covered from fractures of the skull to the treatment of burns. The title of this large volume leaves the reader in doubt as to what "Other Injuries" includes, but once the whole volume has been absorbed one finds that injuries to the abdomen, chest, to the genito-urinary tract, and blood-vessels are all included. It is felt that a better title to this work would have been "Traumatic Surgery".

The Massachusetts General Hospital and the Harvard Medical School are held in admiration by British surgeons, and it is to Boston that the younger generation of surgeons desire to go to see the operative technique of the best of American surgeons.

The first chapter of this book is devoted to the history of the Fracture Clinic of the Massachusetts General Hospital and one is delighted to see the photographs of the great pioneers of American surgery who have worked and carried the flame of surgery through the last four decades—Charles L. Scudder, Phillip D. Wilson, Arthur W. Allen, and M. N. Smith-Petersen—these are indeed names with which to conjure.

The whole work is profusely and beautifully illustrated with clinical photographs, line drawings, and diagrams,

and there can be little doubt that these illustrations do enhance the value of the text.

In the chapter on the management of abdominal injuries one is surprised to find no mention or reference to the name of Sir Gordon Gordon-Taylor, who has made such a great contribution to this subject in two world wars.

As a reference volume this work is excellent, but its price is quite prohibitive in these difficult days of excessive taxation on this side of the Atlantic.

Diffuse Lesions of the Stomach. By IAN J. WOOD, M.D. (Melbourne), F.R.C.P., F.R.A.C.P., Assistant Director of the Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital; and LEON I. TAFT, M.B., B.S., B.Sc. (Melbourne), Pathologist to the Clinical Research Unit, The Royal Melbourne Hospital and Walter and Eliza Hall Institute, Melbourne. $8\frac{1}{2} \times 5\frac{1}{2}$ in. Pp. 86+x, with 35 illustrations. 1958. London: Edward Arnold (Publishers) Ltd. 24s.

THE introduction of radiography during the early part of the present century appeared to obviate the need for gastroscopy, progress of which was halted in consequence. It was not until the late twenties that it was realized that though radiography was of the utmost value in determining the site and nature of localized lesions, it was of little value in the early diagnosis of diffuse lesions of the stomach, and interest in gastroscopy was re-awakened. It was this deficiency on the part of X rays which prompted Schindler to design his flexible gastroscope, which, either in its original form, or in that of one of its modifications, is now in current service in clinics throughout the world. Latterly, however, it was becoming more and more obvious that although it could detect surface changes in the stomach, gastroscopy failed to reveal what was going on underneath the surface, and the pathology of the changes was largely speculative. It was, therefore, a logical step forward that sections of the mucosa should be taken for microscopy. To do this under direct vision, which is the practice in certain clinics to-day, entails a somewhat clumsy instrument, and accordingly Wood and his co-workers at the Walter and Eliza Hall Institute in Melbourne undertook in 1948 to develop a technique of blind biopsy, and to assess its value.

This little book is the outcome of their experience. It contains a full account of the technique involved, and a summary of the findings. The authors discuss very succinctly the microscopic appearances of diffuse changes in the stomach mucosa, and their significance, and attempt to classify chronic gastritis according to a pathological basis. Attention is also given to the significance of atrophic gastritis.

In the early days of blind gastroscopy many were prejudiced against it because they thought it was dangerous, and that in any case it was a bad thing to take a bite out of the stomach wall. The authors have shown, however, that provided reasonable care is taken in instrumentation and in the choice of patients, the risk is negligible, and as they have at the time of publication of this book performed well over a thousand biopsies, their opinion on this matter is authoritative.

An attempt is made to present a clinical picture of the vague symptoms that may be associated with diffuse changes in the stomach, and to rationalize treatment. One of the curious things which every clinician knows about, and which the authors emphasize, is that alkaline powder is a very much more satisfactory medicine in patients with achlorhydria than is dilute hydrochloric acid, which appears to have very little effect. Many will be surprised, perhaps, to read that chronic gastritis develops only rarely during the course of a long duodenal ulcer history, and little mention is made of the comparative frequency with which this lesion is complicated by the development of a chronic gastric ulcer after a lapse of perhaps many years. The authors are rightly very cautious in their assessment of the relationship of chronic gastritis to cancer. The relation in time incidence between gastric atrophy and pernicious anæmia is dealt with at length, and full credit is given to other workers in this field, and particularly to Witts, although the authors do not find themselves in total agreement with him. For example, they differ in that they believe iron deficiency is more likely to follow gastritis than to cause it.

The book is beautifully produced, and contains a large number of excellent photomicrograph reproductions, three of which are in colour. It is indeed rare to find so much valuable information put down so attractively within the small scope of 72 pages of text, and the book can be strongly recommended not only to the specialist gastro-enterologist, but to all practitioners and students of medicine and surgery, whatever their level may be.

Atlas of Tumor Pathology. Section 1, Fascicle 2: **Tumors of the Skin.** By HERBERT Z. LUND, M.D., Director of Laboratories, The Moses H. Cone Memorial Hospital, Greensboro, North Carolina. $10\frac{1}{4} \times 7\frac{9}{16}$ in. Pp. 330, with 265 illustrations. 1957. Washington: Armed Forces Institute of Pathology. $3.00.

THIS large atlas of tumours of the skin is comprehensive and every form and type of skin tumour is described and illustrated. We have learnt to expect something good in this vast work and atlas of tumour pathology, and this monograph has lived up to the reputation of former volumes.

The outstanding feature of this work is the wonderful reproduction of the photomicrographs, which could not be bettered. This makes the work one of great importance from a reference point of view. Surgeons will find a great deal to interest them in this volume, while pathologists will wonder how such consistent uniformity of photomicrographs can be attained.

Atlas de Technique Opératoire: Chirurgie de la Main. By MARC ISELIN, Surgeon, Maison de Nanterre; LUC GOSSE; SERGE BOUSSARD; and DANIEL BENOIST. $8\frac{3}{4} \times 10$ in. Pp. 336, with 692 illustrations. 1958. Paris: Editions Médicales Hammarion. 7000 fr.

No one who visits Dr. Iselin's Clinic in Paris can fail to be impressed by his enthusiasm or the excellence of the little museum on hand surgery that he has built at the Maison de Nanterre. The personality of Iselin shows clearly in this book, which gives detailed guidance on surgical procedures which have been found invaluable in a very wide range of lesions: congenital anomalies, acute hand injuries, contractures due to burns, injury and nerve lesions, infections of the hand and Dupuytren's contracture.

The outstanding feature of the volume is the excellence and clarity of the simple black and white drawings—illustrations which put to shame many of the more elaborate multi-coloured volumes that pour into our libraries from across the Atlantic.

The author has developed the use of the cross-finger flap and shows many variations, including the 'cross-finger *en drapeau*', which have obvious applications. Intramedullary, interosseous, and transarticular pinning is advocated for many conditions other than fixation of fractures or arthrodesis, such as fixation of joints after tendon grafts or transfers. Bipedicled tunnel flaps such as are shown in Figs. 157–163 for the re-surfacing of several

fingers at once are no longer popular in this country. It is somewhat disturbing to see a seven-stage operation described for the transfer of an abdominal flap to the dorsum of the hand in Figs. 173-188; this procedure should normally only require two stages. Furthermore, the use of pinch grafts for the skin cover of a chronic granulating burn of the hand seems rather out of place in a modern book on surgery. Some of the incisions illustrated are misleading. Many are drawn as straight lines across the palm (Figs. 115, 116) rather than curved to follow more accurately the natural flexion creases. The lateral digital incisions shown in Fig. 339 for tendon graft repair are certainly not those recommended by Rank and Wakefield, as the text would have one believe. Those two authors emphasized that the lateral margin of the flap should be well *behind* the line of the digital nerve. Some of the exposures recommended in the treatment of Dupuytren's contracture using multiple transposed flaps (Figs. 633, 638, 648) may be geometrically satisfying but are surely too hazardous for daily use.

However, these are minor criticisms of an important and stimulating book. The chapters on tendon transplants and thumb reconstruction are fascinating. Of exceptional interest are the methods of pollicisation devised by Dr. Jean Gosset and by Dr. le Tac, and the several operations devised by Hilgenfeldt, which are virtually unknown in this country.

Year Book of Orthopedics and Traumatic Surgery, 1957-1958. Edited by EDWARD L. COMPERE, M.D., F.A.C.S., F.I.C.S., Professor and Chairman, Department of Orthopedic Surgery, Northwestern University Medical School. With a section on Plastic Surgery edited by NEAL OWENS, M.D., F.A.C.S., F.I.C.S., Professor of Clinical Surgery, Tulane University School of Medicine. $7\frac{1}{2} \times 5$ in. Pp. 463, with 229 illustrations. 1958. Chicago: The Year Book Publishers Inc. 57s.

THIS *Year Book of Orthopedics and Traumatic Surgery* contains for the first time a separately prepared and edited section on Plastic Surgery by Dr. Neal Owens, Professor of Clinical Surgery at Tulane University School of Medicine. This step is a sensible one, for there is much overlapping of plastic and traumatic surgery, especially in the hand.

There always appears to be something new in orthopædic surgery each year and these new clinical conditions, such as cysts of the os calcis, are well described in this year book.

The illustrations are uniformly good throughout the book. There is no doubt that these year books prove more valuable each year, and any surgeon who undertakes traumatic surgery should certainly possess one.

Actualités Médico-chirurgicales. By R. FONTAINE, G. CORDIER, A. BUSSON, and J. MIALARET. $16{\cdot}5 \times 21{\cdot}5$ cm. Pp. 188, with 40 illustrations. 1958. Paris: Masson et Cie. 2000 fr.

THIS small and pleasantly produced book contains the substance of three of a series of colloquia held by the Paris Faculty of Medicine.

Fontaine and his colleagues deal with the surgery of progressive degenerative arterial disease of the lower limb and consider diagnosis, arteriography, and treatment, in detail. Their results with disobliterative operations and attempts at arteriovenous shunting have not been good, but the by-pass operations are encouraging. One is surprised to read that unilateral adrenalectomy is seriously advocated in progressive Buerger's disease.

Professor Cordier and his associates, in the second section, discuss the treatment of genital prolapse and pouch of Douglas herniation, with special emphasis on the place of vaginal hysterectomy combined with a pelvic floor repair.

Busson and Mialaret, in the final section, deal respectively with the medical and surgical aspects of ulcerative colitis. A tribute to the former is that only 18 per cent of over 500 cases were submitted to the latter. The operative details and post-operative complications are fully considered.

Although authorities are quoted in the text, there is no bibliography; this does detract from the value of this type of monograph, which otherwise deals in an adequate way with three interesting topics.

Gray's Anatomy: Descriptive and Applied. Edited by T. B. JOHNSTON, C.B.E., M.D., Professor Emeritus of Anatomy, University of London; D. V. DAVIES, M.A. (Cantab.), M.B., B.S., Professor of Anatomy, St. Thomas's Hospital Medical School, University of London; and F. DAVIES, M.D., D.Sc. (Lond.), F.R.C.S., Professor of Anatomy, University of Sheffield. Thirty-second edition. $9\frac{3}{4} \times 5\frac{3}{4}$ in. Pp. 1604 + xxiv, with 1329 illustrations, of which 657 are in colour. 1958. London: Longmans, Green and Co. 126s.

THE whole medical profession will rejoice to see the Centenary Edition of this universally read work on anatomy. There can be very few surgeons in the world who have not studied in detail the various editions of *Gray's Anatomy*. This new edition, besides having many new illustrations, has made history insomuch that it is the first book on human anatomy to incorporate electron micrographs in the text.

The untimely death of Professor Whillis in 1955 left Professor Johnston in sole charge of the new edition. He very wisely decided to form an Editorial Board to revise the Centenary Edition and see it through the press. Professor Johnston's choice of co-editors has been wise, and Professors D. V. Davies and F. Davies will add prestige to the work.

Professor Johnston has been associated with *Gray's Anatomy* since 1930, when he was responsible for rejuvenating the work, and he has been at the helm ever since. He had the wise assistance of Professor Whillis from 1942 until his death.

This new Centenary Edition is undoubtedly the best so far produced, with its beautiful coloured pictures, its photomicrographs, and its excellent radiographs, which could not be bettered.

Although *Gray's Anatomy* has always been descriptive and applied, yet never before has the work given more to the surgeon than it does to-day.

We would like to congratulate Professor Johnston and his co-editors on a magnificent achievement.

Anomalies of Infants and Children. By D. MCCULLAGH MAYER, D.D.S., M.D., F.A.C.S., F.I.C.S., Associate Professor of Plastic Surgery, New York Medical College; and WILSON A. SWANKER, M.D., F.A.C.S., F.I.C.S., Professor of Plastic and Aesthetic Surgery, Ankara University, Turkey. $8\frac{1}{4} \times 5\frac{1}{4}$ in. Pp. 454 + x, with 94 illustrations. 1958. New York and London: McGraw-Hill Book Company Inc. 93s.

THIS monograph is devoted to the plastic repair of congenital and other malformations in infants. The book covers a wide range and it covers the whole body. The treatment of burns is very good and comprehensive.

Special consideration has been given to the psychological trauma in connexion with anomalies which both the parent and family experience. In this section considerable attention is given to the facts available for the

explanation of congenital anomalies as an actual hazard to childbirth.

The authors include an account of fluoridation of water in the prevention of dental caries, and the approach to the problem of accidents in children. Some very useful questions are given which doctors should ask the young mother concerning the prevention of accidents.

Congenital Anomalies of the Hand and their Surgical Treatment. By ARTHUR JOSEPH BARSKY, M.D., D.D.S., Attending Surgeon for Plastic Surgery, Mount Sinai Hospital, New York City. $8\frac{1}{2} \times 5\frac{1}{4}$ in. Pp. 165+x, with 77 illustrations. 1958. Springfield, Ill.: Charles C. Thomas (London: Blackwell Scientific Publications). 43s.

THIS is an interesting and important small monograph devoted to congenital anomalies of the hand, and a careful analysis of 165 cases. As a rule, isolated cases of congenital anomalies appear from time to time in the medical literature, but this is the first concerted effort to submit all cases coming under this heading to a careful dissection and a review of the surgical treatment.

There can be little doubt that this book is a permanent record of congenital anomalies of the hand existing at this time. This fact is of importance because in years to come changes or alterations in the patterns can be noted. In view of the concern about the effect of radiation in the production of mutation, it is important to have this record.

The operative technique for the various congenital abnormalities is well described and illustrated.

There is an excellent glossary and an extensive bibliography.

An important reference book on a very special subject.

The Acute Abdomen. By WILLIAM REQUARTH, M.D., Clinical Assistant, Professor of Surgery, University of Illinois College of Medicine. Second edition. $7\frac{3}{4} \times 5\frac{1}{4}$ in. Pp. 313, with 87 illustrations. 1958. Chicago: The Year Book Publishers Inc. 49s.

THE second edition of this essentially practical monograph has been carefully revised and much new material has been added, especially some principles of surgical treatment.

Quite a number of the illustrations are unique in their clearness and the author appears to have the knack of producing black and white drawings which illustrate his thoughts.

The acute abdomen is still a common problem on both sides of the Atlantic and it behoves our younger surgeons to be *au fait* with its many disguises.

This book should prove invaluable to all those studying for higher surgical diplomas, for it gives them a precise picture of the various conditions which may contribute to the clinical condition known as the 'acute abdomen'.

The Rudolph Matas History of Medicine in Louisiana. Edited by JOHN DUFFY. Vol. I. 9×6 in. Pp. 522+xvi, with 14 plates. 1958. Louisiana: Louisiana State University Press. $10.00.

THE name of Matas will always be remembered in surgical circles for the pioneer work he carried out on vascular surgery, and his name will always be kept green by the wonderful collection of manuscripts and pictures dealing with the early history of medicine in Louisiana which he accumulated during his life.

This book is an account of these manuscripts unfolded for the first time by a historian of repute.

In February, 1699, a small band of two hundred souls landed on the shores of the Gulf Coast, giving France her first foothold in what was to become the Louisiana Territory. *The Rudolph Matas History of Medicine in Louisiana*, the first volume of a comprehensive two-volume work, begins with this small group of colonists and traces their medical history through succeeding generations, as Louisiana expanded and flourished, closing with the first quarter of the nineteenth century.

This volume is of intense interest to the medical reader, for it portrays the early primitive hospitals, the horrible epidemics which ravaged the population, and the health of the numerous slaves. From this early beginning the reader can gradually see the first lights of modern medicine. One never realized the magnitude of the yellow fever and cholera epidemics which raged in Louisiana in the eighteenth century.

Rudolph Matas did much for surgery, but he left a wealth of historical medical data which has been put to good use in this volume. We look forward with considerable interest to the second volume of this important historical work.

Fifty Years of Neurosurgery. By ERNEST SACHS, M.D. $7\frac{5}{6} \times 5$ in. Pp. 186, with 15 illustrations. 1958. New York: Vantage Press. $3.50.

AT the present time probably no one except Dr. Sachs has witnessed the birth and development of neurosurgery as an important branch of surgery.

In this interesting and stimulating book, Dr. Sachs paints a vivid picture of the early days of neurosurgery when he studied and helped Sir Victor Horsley at Queen Square. Following this there was a period with Dr. Harvey Cushing and Sir William Osler. An excellent clinical background for anyone who wished to specialize in this new branch of surgery.

Dr. Sachs has published some one hundred and eighty articles in the various medical journals both in America and overseas. He tells his story in a stirring and lively way, and having started this book the reader has to read it through to the end.

Cancer. Edited by RONALD W. RAVEN, O.B.E. (Mil.), T.D., F.R.C.S., Joint Lecturer in Surgery, Westminster Medical School, University of London; Surgeon, Westminster Hospital Teaching Group; Surgeon, The Royal Marsden Hospital. Vol. 3. $9\frac{1}{2} \times 6\frac{1}{4}$ in. Pp. 483 + x, fully indexed, with 165 illustrations. 1958. London: Butterworth & Co. (Publishers) Ltd. 85s.

VOLUME 3 of this now famous work maintains the high standard set by the previous volumes. Further pathological studies complete those discussed in Volume 2, and amongst these a full exposition of the 'marker protein' theory of H. N. Green is given in a chapter entitled "Immunological Aspect of Cancer". The subject of cancer cells in tissue culture is well discussed by Ilse Lasnitzki, and the late Percy Stocks epitomizes much of his work in the Cheshire and North Wales areas on environmental factors in cancer, together with other considerations of a statistical nature.

A section is devoted to epidemiology and the geography of cancer. A valuable contribution by Professor Khanolkar, President of the Union Contre le Cancer, describes cancer in India in relation to habits and customs. Occupational cancer receives consideration together with the medico-legal aspects, and there is a full discussion of methods of cancer detection and 'cytodiagnosis'. One section deals with the long-debated problem of cancer education. The American viewpoint is enthusiastically described by Brewster S. Miller, George Z. Williams, and Cuyler Hammond. The British point of view is well put by John Wakefield, who gives a most reasoned appraisal of the situation and its dangers.

Those who have acquired the previous two volumes in this series have, no doubt, decided to acquire them all, so that to encourage purchase of this work is preaching to the converted. Nevertheless, as in the other volumes, there is contained here well-presented information culled from the vast and often rather inaccessible literature, in a highly assimilable form. The references to each chapter constitute an important bibliography to all aspects of the cancer problem.

Fractures and Dislocations. By GEORGE PERKINS, M.C., M.Ch., F.R.C.S., Consulting Orthopædic Surgeon, St. Thomas's Hospital, London. 9¼ × 6 in. Pp. 363 + viii, with 255 illustrations. 1958. London: University of London—The Athlone Press. 57s. 6d.

THE author of this book is well known for his love of the unorthodox. It is therefore not surprising to find a somewhat provocative text. The preface states that the main purpose of the book is to ensure that patients are not harmed by treatment. But although some of the forms of treatment may cause no harm, their benefit to the patient, except in very special cases, is in considerable doubt. There are many such examples. The advice to treat adult fractures of the femoral shaft by traction without any of the usual splintage is, perhaps, one of the most controversial. It is interesting to know that it is possible to get away with this method, should it be necessary to dispense with a Thomas splint, but it is unlikely to find favour with many practising orthopædic surgeons.

This is a beautifully written book with excellent illustrations; but it must be approached in a critical way, and should not be regarded as 'gospel'. It cannot, therefore, be commended to the student or to the inexperienced, but it should provide amusing, stimulating, and instructive reading for the established traumatic surgeon.

Orthopedic Diseases. By ERNEST AEGERTER, M.D., and JOHN A. KIRKPATRICK, jun., M.D. 9¾ × 6¼ in. Pp. 602 + xii, with 354 illustrations. 1958. Philadelphia and London: W. B. Saunders Co. 87s. 6d.

THIS volume covers an important field dealing with the physiology, pathology, and radiology of bone. These aspects of bone disease have to a certain extent lagged behind other systems in the body.

With the extended use of the phase and electron microscopes modern pathologists are able to give the surgeon more accurate information concerning bone lesions. Bone biopsy has a very definite place in our field of investigation and this, together with modern radiography, is of real value in helping the clinician in difficult differential diagnoses.

All these factors are stressed in this quite original book, and the excellence of the numerous illustrations makes this volume an important addition to surgical literature.

Modern Trends in Anæsthesia. Edited by FRANKIS T. EVANS, M.B., B.S., F.F.A. R.C.S., D.A.; and T. CECIL GRAY, M.D., F.F.A.R.C.S. 9½ × 6½ in. Pp. 318 + x, with 29 illustrations, fully indexed. 1958. London: Butterworth & Co. (Publishers) Ltd. 67s. 6d.

IN recent years great progress has been made in the art and science of anæsthesia, and this interesting book endeavours to describe recent technical advances in detail.

Twenty-two chapters are written by different authors and the book is excellently produced and well illustrated. Of the many interesting chapters, three are exceedingly well written and contain valuable new information. These are: "Hypothermia", by T. Cecil Gray; "Hypnosis", by A. A. Mason; and "Trends in the Mode of Investigation of Anæsthetic Problems", by Dr. Ronald Woolmer. The remaining nineteen chapters adequately cover most aspects of recent advances in anæsthesia, and we recommend this book to all candidates for the F.F.A.R.C.S. and the D.A. examinations. In our opinion, all consultant anæsthetists would be well advised to read this valuable book so as to keep in touch with the many recent developments in modern anæsthesia.

A Text-book of X-ray Diagnosis. By British Authors, in four volumes. Edited by S. COCHRANE SHANKS, C.B.E., M.D., F.R.C.P., F.F.R., Director, X-ray Department, University College Hospital, London; and PETER KERLEY, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., D.M.R.E., Director, X-ray Department, Westminster Hospital, London. Third edition. Vol. III. 9¾ × 7 in. Pp. 883 + xvi, with 802 illustrations. 1958. London: H. K. Lewis & Co. Ltd. 120s.

THE third volume of the third edition of this work contains over 800 illustrations, the majority of which are radiographs illustrating conditions of the alimentary tract, the biliary tract, the urinary tract, and conditions in obstetrics and gynæcology.

To the surgeon this volume should prove of real value as it covers such a large part of the surgical field. The radiographs as a whole are of excellent quality and are beautifully reproduced. All the common, as well as the rare surgical conditions have been included, and this makes the book an important reference work.

This volume is of the same high standard as those already published and the whole work is a credit to an important branch of British medicine.

Operative Surgery. Edited by CHARLES ROB, M.C., M.Chir., F.R.C.S., Professor of Surgery, St. Mary's Hospital, London; and RODNEY SMITH, M.S., F.R.C.S., Surgeon, St. George's Hospital, London. Vol. 8. 11 × 8¾ in. Part xvi: Neurosurgery, pp. 5–57 + xv; Part xvii: Eyes, pp. 5–83; Part xviii: Ear, Nose and Throat, pp. 5–196. Fully illustrated and indexed. 1958. London: Butterworth & Co. (Publishers) Ltd. 110s.

THE eighth volume of this comprehensive work is devoted to the operative surgery of the skull and brain, ophthalmic operations, and those of the nose, ear, and throat. The neurosurgical procedures illustrated are for the most part devoted to traumatic lesions, such as penetrating wounds, extradural and subdural hæmorrhages, and brain abscess.

The various and numerous operative techniques in vogue in ophthalmic and ear, nose, and throat surgery are extremely well illustrated.

This volume is in keeping with its seven predecessors and we have nothing but praise for it.

The whole work is a great credit to British surgery and there can be little doubt that it is, and will remain, the standard work on operative surgery and will be extensively used by surgeons at home and overseas.

Professor Rob and Mr. Rodney Smith must be justly proud of their efforts, and we congratulate them on a great achievement.

Abdominal Operations by the Vaginal Route. By PAUL WERNER, M.D., Late Professor of Gynæcology and Obstetrics, University of Vienna; and JULIUS SEDERL, M.D., Vienna. Translated by L. M. SZAMEK, M.D. 10 × 6¾ in. Pp. 165 + x, with 120 plates. 1958. London: Pitman Medical Publishing Co. Ltd. 65s.

ALTHOUGH surgeons are familiar with the technique of vaginal hysterectomy, few in this country use the vaginal

route for the removal of ovarian cysts, ectopic pregnancy, and tubal conditions. The authors of this volume maintain that vaginal operations possess many advantages, which may be briefly stated as follows. There is easier convalescence, decreased danger of generalized peritonitis, rarer incidence of thrombosis and embolism, greater ease of execution in cases in which extremely fatty abdominal walls are involved, less frequent pulmonary complications, and last but by no means least, the absence of a visible scar. These are no mean advantages and should make the modern gynæcologist take stock of the situation.

We would like to congratulate Dr. Szamek on his excellent translation from the original German. The illustrations which comprise the 120 plates are excellent; they were drawn from actual operations and depict the detailed technique used in the various vaginal operations.

An excellent production.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

Pathology for Students of Dentistry. By GEORGE L. MONTGOMERY, T.D., M.D., Ph.D., F.R.S.E., F.R.F.P.S.(G.), F.R.C.P.E., Professor of Pathology, University of Edinburgh. Second edition. $8\frac{1}{2} \times 5\frac{1}{2}$ in. Pp. 307 + viii, with 134 illustrations. 1958. Edinburgh and London: E. & S. Livingstone Ltd. 40s.

Surgeon at Arms. By DANIEL PAUL and JOHN ST. JOHN. $7\frac{3}{4} \times 5$ in. Pp. 227, with 15 plates. 1958. London: William Heinemann. 16s.

Peripheral Nerve Injuries. By RUTH E. M. BOWDEN, D.Sc., M.B., B.S., L.R.C.P., M.R.C.S., Professor of Anatomy, Royal Free Hospital School of Medicine, University of London. $7\frac{1}{4} \times 4\frac{3}{4}$ in. Pp. 62 + viii, with 30 illustrations. 1958. London: H. K. Lewis & Co. Ltd. 8s. 6d.

Electrolyte Changes in Surgery. By KATHLEEN E. ROBERTS, M.D., Assistant Chief of Medicine, United States Public Health Service Hospital; PARKER VANAMEE, M.D., Assistant Physician, Memorial Hospital for Cancer and Allied Diseases; and J. WILLIAM POPPELL, M.D., Chief, Section of Cardiopulmonary Physiology and Associate, Sloan-Kettering Institute for Cancer Research, New York. $8\frac{1}{2} \times 5$ in. Pp. 113 + x, with 20 illustrations. 1958. Springfield, Illinois: Charles C. Thomas. (London: Blackwell Scientific Publications.) 34s.

A Method of Anatomy. By J. C. BOILEAU GRANT, M.C., M.B., Ch.B., F.R.C.S. (Edin.), Professor Emeritus of Anatomy, University of Toronto. Sixth edition. $9\frac{9}{16} \times 6\frac{7}{16}$ in. Pp. 879 + xxvi, with 862 illustrations. 1958. London: Baillière, Tindall & Cox Ltd. 88s.

A Practice of Thoracic Surgery. By A. L. D'ABREU, O.B.E., Ch.M., F.R.C.S., Surgeon, Queen Elizabeth Hospital, Birmingham. Second edition. $9\frac{3}{4} \times 7$ in. Pp. 619 + viii, fully illustrated. 1958. London: Edward Arnold (Publishers) Ltd. 100s.

Rehabilitation of the Hand. By C. B. WYNN PARRY, M.B.E., M.A., D.M., D.Phys.Med., Specialist in Physical Medicine, Royal Air Force; assisted by N. R. SMYTHE, M.A.O.T., Chairman of the Occupational Therapy Association, Royal Air Force, Chessington; and L. E. BAKER, M.C.S.P., Superintendent Physiotherapist, Medical Rehabilitation Unit, Royal Air Force, Chessington. $9\frac{1}{4} \times 6\frac{1}{4}$ in. Pp. 273 + viii, with 101 illustrations. 1958. London: Butterworth & Co. (Publishers) Ltd. 45s.

An Atlas of Surgery. By F. WILSON HARLOW, M.B., B.S. (Durham), F.R.C.S., Fellow of the International College of Surgeons; with a Foreword by Sir CECIL WAKELEY, Bt., K.B.E., C.B., LL.D., D.Sc., F.R.C.S. $13\frac{1}{4} \times 8\frac{1}{4}$ in. Pp. 363 + xiv, with 1292 illustrations. 1958. London: William Heinemann Medical Books Ltd. 50s.

Neo-natal Paediatrics. Edited by W. R. F. COLLIS, M.D., F.R.C.P., F.R.C.P.I., D.P.H., Director of Department of Paediatrics, Rotunda Hospital, Dublin. $8\frac{1}{2} \times 5\frac{1}{2}$ in. Pp. 301 + xiv, with 33 illustrations. 1958. London: William Heinemann Medical Books Ltd. 30s.

British Obstetric and Gynæcological Practice. Edited by Sir EARDLEY HOLLAND, M.D. (Lond.), F.R.C.P., F.R.C.S., F.R.C.O.G., Consulting Obstetric and Gynæcological Surgeon, London Hospital; and ALECK BOURNE, M.A., M.B., B.Ch. (Cantab.), F.R.C.S., F.R.C.O.G., Consulting Gynæcologist, St. Mary's Hospital, London. Second edition. $9\frac{1}{4} \times 7$ in. Pp. 891 + xii, fully illustrated. 1958. London: William Heinemann Medical Books Ltd. 105s.

Cold Injury, Ground Type. By TOM F. WHAYNE, M.C., U.S.A. (Ret.), Professor of Preventive Medicine, School of Medicine, University of Pennsylvania; and MICHAEL E. DE BAKEY, M.D., Professor of Surgery and Chairman of the Department, Baylor University College of Medicine, Houston, Texas. $9\frac{3}{4} \times 6\frac{1}{4}$ in. Pp. 570 + xxii, with 105 illustrations. 1958. Washington, D.C.: Office of the Surgeon General, Department of the Army. $6.25.

The Cervical Syndrome. By RUTH JACKSON, B.A., M.D., F.A.C.S., Clinical Assistant Professor of Orthopedic Surgery, The University of Texas. Second edition. $8\frac{1}{2} \times 5\frac{1}{4}$ in. Pp. 197 + viii, with 90 illustrations. 1958. Springfield, Ill.: Charles C. Thomas. (London: Blackwell Scientific Publications.) 50s.

Le Reflux Gastro-œsophagien. By P. BLONDET, J. GAILLARD, and P. MICHAUD. $10\frac{1}{4} \times 7\frac{1}{4}$ in. Pp. 158, with 34 illustrations. 1958. Paris: Expansion Scientifique Française. 2600 fr.

Emergency Surgery. By HAMILTON BAILEY, F.R.C.S. (Eng.), F.A.C.S., F.R.S.E., Emeritus Surgeon, Royal Northern Hospital, London; Consulting Surgeon, The Italian Hospital; General Surgeon, Metropolitan Ear, Nose, and Throat Hospital. Seventh edition. $9\frac{3}{4} \times 6\frac{1}{4}$ in. Pp. 1197 + xvi, with 1576 illustrations. 1958. Bristol: John Wright & Sons Ltd. 189s.

A Text-book of Surgery. By PATRICK KIELY, B.Sc., M.D., M.Ch. (N.U.I.), F.R.C.S. (Eng.), Professor of Surgery, University College, Cork; Examiner in Surgery, National University of Ireland. Second edition. $9\frac{3}{4} \times 6$ in. Pp. 1158 + x, with 610 illustrations and 22 coloured plates. 1958. London: H. K. Lewis & Co. Ltd. 63s.

Atlas of Technics in Surgery. By JOHN L. MADDEN, M.D., F.A.C.S., Director of Surgery, St. Clare's Hospital; Associate Clinical Professor of Surgery, New York Medical College; with 62 contributors. $11\frac{3}{4} \times 9$ in. Pp. 648 + xx, with 293 full plates. 1958. New York: Appleton-Century-Crofts Inc. (London: Mayflower Publishing Co.) Approx. £14.

Cancer. Edited by RONALD W. RAVEN, O.B.E. (Mil.), T.D., F.R.C.S., Joint Lecturer in Surgery, Westminster Medical School, University of London. Volume 4, Part VIII, Clinical Aspects. $9\frac{1}{2} \times 6\frac{1}{2}$ in. Pp. 532 + xii, fully indexed, with 173 illustrations. 1958. London: Butterworth & Co. (Publishers) Ltd. 85s.

Clinical Radiology of Acute Abdominal Disorders. By BERNARD S. EPSTEIN, M.D., Chief, Department of Radiology, The Long Island Jewish Hospital, New York. $10 \times 6\frac{3}{4}$ in. Pp. 352, with 406 illustrations on 224 figures. 1958. London: Henry Kimpton. 112s. 6d.

Head Injuries. By E. S. GURDJIAN, M.D., Professor of Neurological Surgery, Wayne State University College of Medicine; and J. E. WEBSTER, M.D., Associate Professor of Neurological Surgery, Wayne State University College of Medicine. $9\frac{1}{4} \times 6$ in. Pp. 482, with 108 illustrations. 1958. London: J. & A. Churchill Ltd. 100s.

The Esophagus. Medical and Surgical Management. By EDWARD D. BENEDICT, M.D., F.A.C.S., Assistant Clinical Professor of Surgery, Harvard Medical School; and GEORGE L. NARDI, M.D., F.A.C.S., Clinical Associate in Surgery, Harvard Medical School. $9\frac{3}{4} \times 6\frac{1}{2}$ in. Pp. 390, with 108 illustrations. 1958. London: J. & A. Churchill Ltd. 105s.

Surgery of the Head and Neck. By ROBERT A. WISE, M.D., Associate Clinical Professor of Surgery, University of Oregon Medical School; and HARVEY W. BAKER, M.D., Clinical Instructor of Surgery, University of Oregon Medical School. $8\frac{1}{4} \times 5\frac{1}{2}$ in. Pp. 319, fully illustrated. 1958. Chicago, Ill.: Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 73s.

Emergency War Surgery. N.A.T.O. Handbook. Prepared for use by the Medical Services of N.A.T.O. Nations. $7\frac{3}{4} \times 5$ in. Pp. 411 + xii. 1958. Washington, D.C.: United States Government Printing Office. $2.25.

Surgery of the Sympathetic Nervous System. By Sir JAMES PATERSON ROSS, K.C.V.O., LL.D., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., Director of the Surgical Professorial Unit, St. Bartholomew's Hospital, London. Third edition. 9×6 in. Pp. 170 + xii, with 51 illustrations. 1958. London: Baillière, Tindall & Cox Ltd. 35s.

Varied Operations. An Autobiography. By Hon. HERBERT A. BRUCE, M.D., F.A.C.S., L.R.C.P., F.R.C.S. (Eng.). $9\frac{1}{4} \times 6$ in. Pp. 366 + xviii, with 9 plates. 1958. Toronto: Longmans, Green & Co. $6.00.

Ptoses Abdominales et Prolapsus Pelviens. By LUCIEN DIAMANT-BERGER. $9\frac{1}{2} \times 6$ in. Pp. 194, with 119 illustrations. 1958. Paris: Doin.

Modern Trends in Surgical Materials. Edited by LEON GILLIS, M.B.E., M.Ch. (Orth.), F.R.C.S. (Eng.), F.R.C.S. (Edin.), D.L.O., Consultant Surgeon, Queen Mary's (Roehampton) Hospital, East Ham Memorial Hospital and St. John's Hospital, London. $9\frac{1}{2} \times 6\frac{1}{2}$ in. Pp. 266 + xii, with 96 illustrations. 1958. London: Butterworth & Co. (Publishers) Ltd. 72s. 6d.

The Management of Emergencies in Thoracic Surgery. By JOHN BORRIE, M.B.E., Ch.M., F.R.C.S. (Eng.), F.R.A.C.S., Thoracic Surgeon, Dunedin Hospital and Southern Metropolitan Region, New Zealand. $9\frac{1}{2} \times 6\frac{1}{2}$ in. Pp. 340 + xii, fully illustrated. 1958. New York: Appleton-Century-Crofts Inc. $10.00.

Outline of Fractures. By JOHN CRAWFORD ADAMS, M.D., F.R.C.S., Consultant Orthopaedic Surgeon, St. Mary's Hospital, London. Second edition. $8\frac{1}{2} \times 5\frac{1}{2}$ in. Pp. 268 + viii, with 237 illustrations. 1958. Edinburgh and London: E. & S. Livingstone Ltd. 27s. 6d.

Comparative Anatomy and Physiology of the Nose and Paranasal Sinuses. By Sir VICTOR NEGUS, Hon. D.Sc. (Manch.), M.S. (Lond.), F.R.C.S. (Eng.), Consulting Surgeon to the Ear, Nose, and Throat Department, King's College Hospital. $9\frac{3}{4} \times 6\frac{1}{2}$ in. Pp. 402 + xv, with 178 illustrations. 1958. Edinburgh and London: E. & S. Livingstone Ltd. 70s.

Year Book of Cancer, 1957–1958. Edited by RANDOLPH LEE CLARK, jun., B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), Director and Surgeon in Chief, The University of Texas; and RUSSELL W. CUMLEY, B.A., M.A., Ph.D., Director of Publications, The University of Texas. $7\frac{1}{2} \times 5$ in. Pp. 523, with 191 illustrations. 1958. Chicago, Ill.: The Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 60s.

Urology in Outline. By T. L. CHAPMAN, Ch.M., F.R.C.S. (Eng.), F.R.F.P.S. (Glas.), Honorary Clinical Lecturer in Urology (University of Glasgow), and Urological Surgeon, Victoria Infirmary, Glasgow. $8\frac{3}{4} \times 6$ in. Pp. 176 + viii, with 138 illustrations. 1959. Edinburgh and London: E. & S. Livingstone Ltd. 27s. 6d.

Tumours of the Bladder. Edited by DAVID M. WALLACE, O.B.E., M.S., F.R.C.S., Surgeon, St. Peter's, St. Paul's, St. Philip's Hospitals; Senior Lecturer, Institute of Urology, University of London. $9\frac{3}{4} \times 6\frac{1}{2}$ in. Pp. 352 + xvi, with 202 illustrations. 1959. Edinburgh and London: E. & S. Livingstone Ltd. 60s.

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